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DIABETES AND PREGNANCY*

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THE purpose of this paper is to present the results of our experience with 140 pregnancies in diabetes from 1932 to September 1, 1950, with special reference to factors influencing fetal mortality. The first 18 cases of this series have been previously reported in an earlier communication.[1] Except for a small group of 14 patients treated with diethylstilbestrol by mouth,[2] the patients have had no specific treatment other than careful medical management of their diabetes, and delivery according to the obstetric indications, as discussed by Hurwitz and Irving[1] in 1937. Insulin therapy has reduced the fetal mortality from about 50 per cent to about 20 per cent, but it still remains approximately five times that in the nondiabetic patient. Diabetes, therefore, unlike some other chronic diseases such as tuberculosis in pregnancy, seems to have a deleterious effect upon the fetus. It is interesting that this effect occurs even before the onset of diabetes; Miller, Hurwitz and Kuder[3] found that the fetal and neonatal mortality was as high during the five-year period immediately preceding the onset of diabetes as after the diagnosis had been established. It is apparent that the main problem in diabetic pregnancies is the high fetal mortality, since the maternal mortality is the same as that in nondiabetic pregnancies. In this series the maternal mortality was zero. Before the factors influencing fetal mortality are discussed, it might be well to describe the methods of diagnosis and management of diabetes during pregnancy.

DIAGNOSIS

That sugar often occurs in the urine during pregnancy is well known. This has been ascribed to a lowering of the renal threshold for glucose, or to lactosuria. We found early that fermentation tests to differentiate lactose from glucose were of no practical aid in diagnosis, because all urines showing a large amount of reducing substances had positive fermentation tests. We have made the diagnosis of diabetes during pregnancy only after obtaining high postprandial blood sugar levels. Of 25 normal pregnant patients upon whom serial glucose tolerance tests were done, 81 per cent showed high two-hour levels (over 120 mg. per 100 cc. by the Folin-Wu method) at some time during pregnancy.[4] It is obvious, therefore, that one cannot use a high two-hour level as diagnostic of diabetes during pregnancy. High peaks are also not uncommon, and an occasional patient may show a high peak and high two-hour level with a normal or low three-hour level. Such a patient reveals glycosuria but is not diabetic; this phenomenon has been referred to as high alimentary hyperglycemia.[4] These patients do well, and offer no complications during pregnancy. We have used a high blood sugar level (over 120 mg. per 100 cc.) at the end of three hours of an oral glucose tolerance test (100 gm. of glucose by mouth) as diagnostic of diabetes. A few patients so diagnosed have reverted to a normal configuration when retested several months postpartum. It is obvious that if the criterion for diagnosis of diabetes during pregnancy were less stringent than as stated above, there would be a larger number of extremely mild (or nonexistent) cases, which would have as a whole a favorable effect upon the fetal-mortality statistics of diabetic pregnancies.

METHOD OF MANAGEMENT

When the diagnosis of diabetes is made, or when a new diabetic patient comes to the Diabetic Clinic, the patient is placed on a diet of 180 gm. of carbohydrate or more, 75 gm. of protein or more and fat, according to her nutritional needs. If glycosuria is not controllable by diet alone, protamine zinc insulin and regular insulin separately administered are prescribed in amounts sufficient to keep the urine as sugar free as possible without provoking hypoglycemia. More recently suitable patients have been adequately controlled with NPH insulin. The patient is seen at weekly intervals during pregnancy, since there is usually an increased need for insulin, especially in the second and third trimesters.

In the latter part of this series, the patients were hospitalized for a few days at approximately the

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thirty-fifth week of pregnancy, when a decision was made concerning the type of delivery. Many patients were readmitted between the thirty-seventh and thirty-ninth weeks for observation and induction of labor, if indicated. If there were clearcut obstetric indications, such as toxemia with an unfavorable cervix, placenta praevia and cephalopelvic disproportion, a cesarean section was done. That a cesarean section was by no means routine is shown by the occurrence of only 20 such procedures in the entire group of 140 pregnancies (Table 1).

TABLE 1. *Clinical Management of the Diabetic Patient During Pregnancy.*

1. *Diet*: carbohydrate, at least 180 gm.; protein, 75 gm. or more; and fat, according to state of nutrition.
2. *Insulin*: both protamine zinc insulin and regular insulin to make the urine as close to sugar free as possible without provoking hypoglycemia, the increased need of insulin during pregnancy being borne in mind.
3. *Stilbestrol*: orally, according to schedule of Smith and Smith, given only to patients arriving in clinic before the 20th week of pregnancy (others are used as controls).
4. *Weekly clinic visits* during entire pregnancy, to ensure good diabetic control and to watch weight.
5. *Admission at 35th week* for study and evaluation by obstetric and medical staff; decision is then made as to time and method of delivery.
6. *Pelvic delivery* whenever possible.

Diabetic management during labor is surprisingly easy. Most patients in labor have taken their morning protamine zinc insulin. If labor is prolonged, there may be a tendency to hypoglycemia, so that small amounts of fruit juices should be administered during early labor, and glucose given intravenously during the latter part of labor. If acetonuria develops as a result of prolonged labor and lack of food intake (acetonuria occurs more readily in pregnant than in nonpregnant patients) additional glucose and insulin may be necessary. There are usually no difficulties with the labor of the diabetic mother. The usual analgesics and a low spinal anesthesia are used before delivery. After the baby is born, blood sugar determinations are made on the umbilical-cord blood, the newborn infant's capillary blood and the mother's venous blood. The mother's insulin dosage is watched carefully because there is often a sharp drop in the immediate post-partum period to a level comparable to the amount taken prior to pregnancy. The newborn infant's blood sugar level may be extremely variable, so that the fact that an infant has a low blood sugar level does not necessarily mean an insulin reaction. No attempt is made to administer glucose by mouth during the first forty-eight hours of life, since the baby is in need of dehydration. Only 1 newborn infant had what appeared to be an insulin reaction, and this was promptly relieved by glucose intravenously.

Effect of Severity and Duration of Diabetes on Fetal Mortality

It has been considered that patients with severe diabetes or with diabetes of long duration suffer a progressively higher fetal mortality than those with mild diabetes or of short duration. Table 2 shows our classification according to severity and duration.

TABLE 2. *Effect of Severity and Duration of Diabetes on Fetal Mortality.*

Severity	No. of Cases	No. of Deaths	Duration	No. of Cases	No. of Deaths
Mild (no insulin required)	45	4 (9%)	Onset with pregnancy	53	6 (11%)
Moderate (1–20 units of insulin required)	10	3 (30%)	2 mo.–5 yr.	47	15 (32%)
Moderately severe (21–50 units of insulin required)	22	9 (41%)	6–10 yr.	25	8 (32%)
Severe (more than 51 units of insulin required)	63	16 (25%)	11–15 yr.	11	2 (18%)
			16–20 yr.	3	1 (33%)
			More than 21 yr.	1	0
Totals	140	32		140	32

Our figures reveal a much lower fetal mortality in the groups of diabetic mothers requiring no insulin or in those in whom the onset of the disease occurred during pregnancy than in the groups of patients requiring insulin or those whose diabetes preceded pregnancy. However, beyond this there appears to be no statistical difference in fetal mortal-

TABLE 3. *Incidence of Toxemia in Relation to Severity and Duration of Diabetes.*

Severity of Diabetes	Cases of Diabetes	Cases of Toxemia	Duration of Diabetes	Cases of Diabetes	Cases of Toxemia
Mild (no insulin required)	45	5 (11%)	Onset with pregnancy	53	6(11%)
Moderate (1–20 units of insulin required)	10	2 (20%)	2 mo.–3 yr.	47	15 (32%)
Moderately severe (21–50 units of insulin required)	22	11 (50%)	6–10 yr.	25	10 (40%)
Severe (more than 51 units of insulin required)	63	22 (35%)	11–15 yr.	11	5 (46%)
			16–20 yr.	3	3 (100%)
			More than 21 yr.	1	1 (100%)
Totals	140	40 (29%)		140	40 (29%)

ity between patients with mild and those with severe diabetes or between those with cases of short and those of long duration. White[5] reported in her series that 52 per cent of the fetal mortality was associated with diabetes of over ten years' duration, whereas her cases were equally divided between those under and those over ten years in duration.

TABLE 4. *Fetal Mortality in Toxemic and Nontoxemic Cases.**

TYPE OF PREGNANCY	NO. OF CASES	NO. OF FETAL DEATHS	FETAL MORTALITY %
Nontoxemic	100	20	20
Toxemic	40	12	30
Totals	140	32	

*There were 38 cases of pre-eclampsia in the mother, with 10 fetal deaths, and 2 cases of eclampsia, with no fetal deaths.

degeneration. Again, it should be emphasized that the fetal mortality is high five years before the actual onset of diabetes.

EFFECT OF TOXEMIA ON FETAL MORTALITY

Our experience confirms that of others that there is an increased incidence of toxemia in diabetic pregnancies (Table 3).

The incidence of 29 per cent is about four times that in nondiabetic pregnancies (7 or 8 per cent). The incidence of 11 per cent occurring in mild diabetes or in cases in which the disease was discovered during pregnancy is only slightly higher than that in nondiabetic pregnancies. The patients with severe diabetes and those with disease of long duration showed a threefold to fourfold increase in the incidence of toxemia. That this increase is not necessarily related to the degree of severity is shown by the fact that the incidence of toxemia was no higher in the severe group (35 per cent) than in the moderately severe group (50 per cent). A higher incidence of toxemia was generally found when the diabetes was of longer duration. The incidence of toxemia among the cases resulting in fetal deaths was higher than that in the cases in which the fetus survived (Table 4). The relation of toxemia to intrauterine death is not completely clear. As shown below, it is only one of several factors that

TABLE 5. *Analysis of Fetal Deaths.*

DURATION OF PREGNANCY	STILLBIRTHS	NEONATAL DEATHS	CASES OF TOXEMIA IN MOTHER	LETHAL MALFORMATIONS	OTHER CAUSES OF DEATH	POSSIBLE OBSTETRIC CAUSE OF DEATH	CASES WITH NO APPARENT CAUSE OF DEATH	TOTAL FETAL DEATHS
wk.								
32	1	3	1	.....	Erythroblastosis — 1 case Prematurity — 1 case Intracranial hemorrhage — 1 case	.....	1	4
33	0	0	0	.....	.....	.....	0	0
34	3	0	2	.....	.....	Prolapsed umbilical cord in twin breech presentation — 1 case	2	3
35	4	1	2	Congenital heart disease (tetralogy of Fallot) — 1 case	Erythroblastosis — 1 case	.....	3	5
36	8	3	4	Anencephaly — 1 case	Miller–Wilson triad* and subarachnoid hemorrhage — 1 case Miller–Wilson triad* — 1 case Intraperitoneal hemorrhage — 1 case Von Gierke's disease and Miller–Wilson triad* — 1 case	.....	6	11
37	3	0	2	Hydrocephalus and erythroblastosis — 1 case	.....	22-hour labor and prolapse of umbilical cord — 1 case	1	3
38	2	1	0	Congenital alveolar dysplasia — 1 case	.....	.....	2	3
39	0	1	0	.....	Subdural hemorrhage — 1 case	.....	0	1
40	1	1	1	Congenital heart disease (triloculare biventriculare) —1 case	.....	27-hour labor and intrauterine colon bacillus infection — 1 case	..	2
Totals	22	10	12	5	9	3	15	32

*Defined as cardiac enlargement, erythropoiesis of liver and hyperplasia of pancreatic islet cells.

Our findings, therefore, tend to agree with this conclusion. Other circumstances, as yet not clear, more important than the severity and duration of diabetes appear to influence the increased fetal mortality. The degree of maternal vascular degeneration may be one of several such factors. That still other factors are present is indicated by the frequent occurrence of sudden intrauterine deaths in well controlled diabetic pregnancies without evidence of vascular

appear to contribute to the high fetal mortality occurring in diabetic pregnancies.

Analysis of Fetal Deaths

In this group of 140 pregnancies in diabetic patients there were 32 fetal deaths, a mortality of 23 per cent. Excluded from this series are 2 therapeutic abortions (indications were severe nephritis and severe hypertension, respectively) and 5 spontaneous abortions. This small number (3 per cent) is due to the fact that many patients arrive at the clinic when their pregnancies are moderately well advanced. Therefore, those with spontaneous abortions are only occasionally seen.

Table 5 shows the distribution of causes of all the fetal deaths in this series. There were 22 intrauterine and 10 neonatal deaths. The causes of death in the latter group were as follows: congenital heart disease with triloculare biventriculare; subarachnoid hemorrhage and Miller–Wilson triad[6]; intrauterine pneumonia and Miller–Wilson triad; tetralogy of Fallot; subdural hemorrhage; erythroblastosis and kernicterus; intracranial hemorrhage; congenital alveolar dysplasia; prematurity with primary atelectasis; and intraperitoneal hemorrhage. There were 5 lethal congenital anomalies and 9 other cases in which the cause of death was certain. There were only 3 deaths that in retrospect might have been considered obstetric and therefore preventable. In 15 out of 22 stillbirths no cause of death could be found. Twelve of these 15 deaths occurred during the period of the thirty-fourth to the thirty-seventh week. Although 10 of 12 cases of toxemia occurred during this same period, only 4 cases showed close association between this complication and intrauterine death.

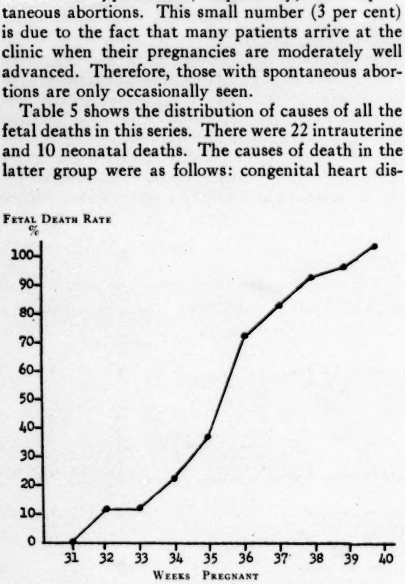

Figure 1. *Cumulative Fetal Death in Third Trimester.*

It is of interest that 72 per cent (23 stillbirths or neonatal deaths) of fetal deaths had already occurred by the end of the thirty-sixth and 81 per cent by the end of the thirty-seventh week (Fig. 1). If premature delivery at the thirty-eighth week had been sought, as advocated by some, only 4 deaths occurring beyond this point might have been averted. Two additional deaths were due to congenital anomalies incompatible with life (Table 5). Furthermore, there was an abrupt increase in the cumulative fetal deaths during the thirty-sixth week to 72 per cent from 38 per cent during the preceding week. The obvious implication is that an even earlier premature delivery than usually advocated, probably during the thirty-fifth week, might decrease intrauterine deaths. Whether this would result in an increase in neonatal deaths from prematurity cannot be answered at present. In addition, 6 of 11 deaths occurring during the thirty-sixth week and 11 of 19 during the thirty-fourth to the thirty-sixth week were stillbirths in which no cause of death was demonstrable.

Of these 11 stillbirths, only 4 were closely associated with maternal toxemia, leaving 7 without any obvious cause of death, either fetal or maternal. Thus, if the majority of intrauterine deaths cannot be anticipated, this may suggest termination of pregnancy at a time prior to its peak evidence as a routine procedure, but before this can be concluded its effect on neonatal mortality should be determined.

Hormonal Therapy

The hormonal treatment of diabetes in pregnancy is based upon the original work of Smith et al.,[7] who showed that hormonal imbalance (abnormal rise in serum chorionic gonadotrophins and fall in urinary estrogens and pregnandiol excretion) was in progress for some weeks prior to fetal death or maternal toxemia. They further demonstrated that prophylactically administered oral diethylstilbestrol counteracted this imbalance.[8] For the past five years we have been treating all patients arriving before the twentieth week of pregnancy with diethylstilbestrol by mouth according to dosage schedule B. Starting with 5 mg. of stilbestrol at the seventh and eighth weeks of pregnancy, the dosage is progressively increased every two weeks so that by the thirty-fourth week the daily dosage is 150 mg. The last medication is taken at the end of the thirty-fifth week. Patients arriving at the clinic later than the twentieth week of pregnancy have constituted a control group.

There were 14 patients in the treated group for a total of 16 pregnancies, and 23 patients in the control group for a total of 26 pregnancies. Both groups were comparable so far as severity and duration of diabetes were concerned. However, a few in the control group were noted to be careless about their diabetes because of lack of intelligence or personal indifference. That these patients sought

obstetric and medical care for the first time after five months of pregnancy is somewhat indicative of personal carelessness. This has led us to believe that our method of setting up controls for these observations (which was thought necessary because of the small number of diabetic patients seen each year in this clinic) is not satisfactory. In the treated group there were 3 fetal deaths (19 per cent) and 2 cases of maternal toxemia (18 per cent), both mild pre-eclampsia; in the control group there were 9 fetal deaths (35 per cent) and 7 cases of maternal toxemia (27 per cent), 1 of which was eclampsia. In the entire series, exclusive of the treated group and inclusive of the control group, there were 29 fetal deaths in 124 pregnancies, an incidence of 23 per cent, and 38 cases of maternal toxemia, an incidence of 31 per cent. The causes of fetal death in the treated group were hydrocephalus, congenital alveolar dysplasia, and prolapsed cord in twin breech presentation; there was no case of unexplained intrauterine death. On the other hand, in the control group 7 of 9 deaths could not be explained. The 2 remaining deaths were due to tetralogy of Fallot and erythroblastosis with kernicterus.

Our treated series of only a few patients comprises a part of a larger series, which will be reported in the future. Neither the treated nor the control group contains sufficient numbers of patients to make valid statistical analysis. The total number of untreated patients mentioned above reflected more or less the same trend shown in the control series. A preliminary impression is that pregnant diabetic patients treated with diethylstilbestrol by mouth early in pregnancy may show a decreased incidence of fetal deaths and maternal toxemia.

It is impossible to evaluate correctly the efficacy of hormonal treatment without rigid controls. The ideal method is to treat alternate comparable cases with hormonal therapy. The same obstetrician or team of obstetricians should handle both groups without any knowledge of which patients are receiving hormonal therapy. Obviously, such a study can be carried out only in a clinic handling large numbers of diabetic pregnant patients annually.

Summary and Conclusions

Experience with 140 diabetic pregnant patients over an eighteen-year period is discussed from the standpoint of diagnosis and management during pregnancy.

The incidence of fetal mortality could not be closely correlated with the severity or duration of maternal diabetes, except for a lower incidence found in mild diabetes or in diabetes discovered during pregnancy.

The incidence of toxemia (29 per cent) was increased as compared to that in nondiabetic women (7 or 8 per cent). A slightly higher incidence of toxemia was noted in cases in which intrauterine or neonatal deaths occurred.

The net fetal mortality was 23 per cent, 72 per cent of which occurred before the thirty-seventh week. Whether or not earlier delivery than previously advocated will result in more live babies or more neonatal deaths from prematurity cannot be answered at present.

Preliminary studies on a small group of patients treated orally with diethylstilbestrol appear to show a decreased incidence of fetal mortality and maternal toxemia.

An ideal method of study for evaluating hormonal therapy is outlined.

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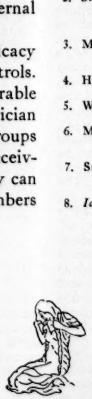

ASSOCIATION OF SPONTANEOUS MEDIASTINAL EMPHYSEMA AND ACUTE MYOCARDIAL INFARCTION*

Report of Two Cases

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SPONTANEOUS mediastinal emphysema was first described as a clinical entity by Hamman[1] a little more than a decade ago. Although the initial pathological report by Laënnec[2] appeared in 1879, the clinical characteristics and diagnostic features were not elucidated until Hamman compiled his observations on 6 cases. A review of the literature reveals 58 cases reported, giving evidence of increasing awareness of the condition. All authors have emphasized the importance of recognizing this benign condition in the adult to differentiate it from other more serious diseases, notably coronary occlusion, pericarditis, pulmonary embolism and dissecting aneurysm of the aorta. In the light of the 2 cases of spontaneous mediastinal emphysema associated with myocardial infarction reported below, the previous appraisal of its universally innocuous course needs to be questioned.

CASE REPORTS

CASE 1. F. Y., a 61-year-old man, entered the hospital on May 2, 1949, complaining of chest pain. He had been well until 2 days before, when he suddenly felt pain across the entire anterior portion of the chest while laying bricks. The pain, which was described as "knife-like" but nonconstricting, radiated to the shoulders, arms, teeth and ears. The pain lasted for 5 minutes and was accompanied by slight dyspnea and weakness. He returned home, where he remained throughout the following day without further pain, but with some residual weakness. He returned to work the next day and experienced a recurrence of the same chest pain, which continued intermittently throughout the day, being aggravated by exertion and relieved by rest. Later in the day the pain became more severe and persistent, at which point the patient was seen by his family physician, who administered "two shots," after which the patient vomited. The history was otherwise unrevealing, with the exception of minimal dyspnea on exertion for the past 5 years and alleged "liver trouble" 20 years previously. The details of the latter complaint were not elicited.

Physical examination revealed an obese, somewhat plethoric man, who appeared alert, apprehensive and acutely ill. The chest showed an increased anteroposterior diameter but was symmetrical, with normal fremitus and resonance throughout. A few moist inspiratory rales were heard at both bases. The heart was not enlarged to percussion, and there were no palpable thrills. The heart tones were distant; there was a regular tachycardia, with what was interpreted as a suggestive gallop rhythm at the apex. The findings were otherwise negative.

The blood pressure was 150/100, the temperature was 97.4°F., the pulse rate 140 per minute, and the respirations 28.

Initial laboratory examinations on May 3 showed a clear, yellow urine, which gave a ++ reaction for sugar and contained a trace of albumin and urobilinogen. The blood Kahn test was inconclusive, and the blood Wassermann test was doubtful. The nonprotein nitrogen was 36 mg., and the fasting blood sugar 139 mg. per 100 cc. Examination of the blood revealed a red-cell count of 5,420,000, with a hemoglobin of 105 per cent (16.4 gm.), and a white-cell count of 15,350, with 88 per cent neutrophils, 6 per cent lymphocytes and 6 per cent monocytes. The sedimentation rate was 19 mm. per hour, and the hematocrit 51 per cent.

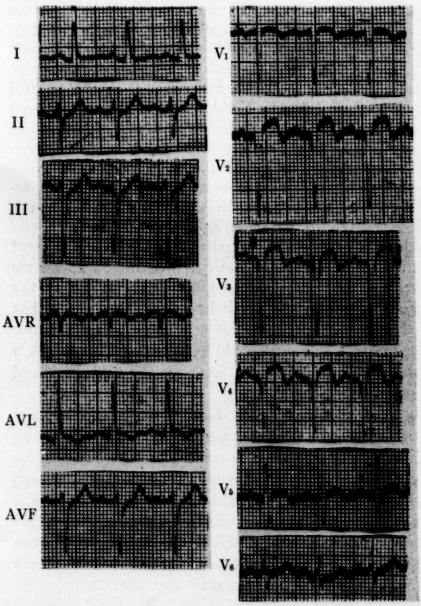

FIGURE 1. *Electrocardiogram in Case 1, Taken on May 2, 1949.*

An electrocardiogram (Fig. 1) taken at the time of admission showed a sinus rhythm at a rate of 120, left-axis deviation, a PR interval of 0.16 second and a QRS complex of 0.10 second. The Q waves were small in Leads 1 and AVL, and the T wave was flattened in Lead 1 and inverted in Lead AVL. A small R wave was present in Lead V_1, but there were no R waves in Leads V_2, V_3 and V_4. The transition zone was between Leads V_4 and V_5. Significant elevations of the ST segments, measuring 2 mm., were noted in Leads V_2, V_3, V_4 and V_5, with depressed ST segments in Leads 2 and 3. Diphasic to inverted T waves were present in Leads V_2, V_3 V_4 and V_5. The graph was interpreted as showing a horizontal heart with clockwise rotation and a probably acute anterior myocardial infarction.

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Routine treatment including oxygen and morphine was instituted on May 3. The patient showed improvement, but continued to have some dyspnea and nausea. Early the following morning he was noted to have a crepitant swelling of the suprasternal, supraclavicular, cervical and facial regions, principally on the left side, which over a period of an hour progressed to massive proportions bilaterally (Fig. 2), with increased dyspnea. Hyperresonance was present over the sternum, and the heart tones were distant. Because of the extreme dyspnea it was decided to attempt aspiration of the subcutaneous emphysema. By means of a thoracentesis aspirator, 500 cc. of air was withdrawn from the subcutaneous region of the anterior triangle of the neck. This resulted in immediate decompression of the orbital and facial emphysema and remarkable relief of the dyspnea. Subsequently, the patient appeared extraordinarily improved. The pulse rate decreased to 92 per minute, and the respirations to 18; the temperature was 99.2°F. The patient's condition continued to improve until midday, when while sitting up in bed talking to his wife, he suddenly collapsed and died.

FIGURE 2. *Appearance of Patient in Case 1, Showing Marked Subcutaneous Emphysema.*

At post-mortem examination* on May 5, when the sternum was removed, the connective tissue over the anterior portion of the parietal pericardium was seen to contain air bubbles that measured 3 to 8 mm. in diameter. The surrounding tissue was found to be crepitant. Examination of the pleural cavities failed to reveal any signs of pneumothorax. The right pleural cavity contained many focal fibrous adhesions, but the left was free of fluid or adhesions.

Examination of the neck disclosed the presence of a few small air bubbles and slight crepitation of the connective tissue on the right side.

*Performed by Dr. John Lunseth.

The lungs were hypercrepitant, except for the left upper lobe, which was subcrepitant. The origin of the interstitial emphysema could not be found. On section, the surfaces of the lobes, excluding the right upper, which was bluish gray and moist with a red fluid, were pinkish tan and slightly moist, with a pink, frothy fluid. The trachea and bronchi were slightly injected and contained a red, frothy fluid. The tracheobronchial lymph nodes were anthracotic and firm.

The heart weighed 400 gm. The epicardial fat was increased, and the surface was smooth. The chambers were dilated, and the apex was formed chiefly by the left ventricle. The consistence of the myocardium was reduced. The right atrium was slightly dilated, and the right ventricle moderately dilated. On section the myocardium of the lower half of the left side of the septum and the lower half of the anterior lateral wall of the left ventricle showed a purple-red mottling of the inner half of the myocardial wall. These purple areas were soft and had a smudgy appearance. The valves appeared normal. The coronary arteries revealed numerous yellow nonulcerated plaques along the left descending coronary artery and a few in the left circumflex branch, but nowhere could any occlusion of a vessel be demonstrated.

Microscopical examination of the heart demonstrated a thickened epicardium containing round cells, with polymorphonuclear-cell infiltration and vascularization. The myocardial fibers were hypertrophied. In many areas there was fragmentation of the fibers, separation and marked interstitial infiltration by polymorphonuclear cells. Many fibers showed loss of nuclei, pyknosis of nuclei and alteration of staining of the cytoplasm.

There was marked congestion of the blood vessels. There was marked perivascular and peribronchial anthracosis. The alveoli contained a few red cells and round cells.

CASE 2. A. T., a 64-year-old retired Polish foundry worker, entered the hospital on January 24, 1950, complaining of dyspnea. His illness had begun 3 days before with a chill, questionably shaking in character, and the onset of cough productive only of a small amount of whitish sputum. There had been no subsequent chills, but the dyspnea had increased slightly. The temperature, taken at home on the day of admission, was reported to have been 100°F.

The past history revealed that in July, 1949, the patient had experienced an anginal type of distress, which shortly disappeared, and he had remained fairly well except for moderate shortness of breath on exertion.

Physical examination showed the patient to be well developed, well nourished and moderately dyspneic, exhibiting audible wheezing respiration. There was slight xanthelasma of the eyclids, and the fundi revealed minimal sclerosis of the arterioles. The chest presented an increased anteroposterior diameter, and on auscultation there were scattered wheezes and rhonchi, with a few rales at both bases. The heart appeared slightly enlarged to percussion; the tones were of good quality and of fair intensity with a regular rhythm. The aortic second sound equaled the pulmonic; no murmurs were detected. The abdomen was scaphoid, and the liver edge was palpable 8 cm. below the costal margin. There was no edema, and the remainder of the examination was negative.

The temperature was 100°F. by rectum, the pulse 100, and the respirations 28. The blood pressure was 140/94.

The urine was clear, with a specific gravity of 1.020, and gave a + reaction for albumin. Examination of the blood showed a red-cell count of 4,010,000, with a hemoglobin of 78 per cent (12.1 gm.), and a white-cell count of 5400, with 68 per cent neutrophils, 1 per cent eosinophils, 1 per cent basophils, 28 per cent lymphocytes and 2 per cent monocytes. A blood serologic test was negative. The nonprotein nitrogen was 40 mg., and the total protein 6.1 gm. per 100 cc. An anteroposterior chest film revealed increased densities at both bases compatible with passive congestion.

The patient was placed on cardiac management and received 300,000 units of penicillin. The temperature returned to normal on January 25, but he continued to show moderate dyspnea and orthopnea. At approximately 6 p.m. on the following day, increased dyspnea was noted. Examination revealed marked diaphoresis; the skin was cool, and the pulse was regular at a rate of 80 per minute. The blood pressure was 134/105. There was a striking asymmetry of the face, with a small, walnut-sized swelling over the left cheek. On palpation this mass revealed crepitation, which was also palpable over the entire left lateral aspect of the face to the

level of the ear and extending down the neck and over both supraclavicular fossae. Hyperresonance was noted on percussion over the sternum and precordium. The heart tones were distant and regular at 80 per minute, with an occasional premature systole. A soft, rub-like sound was heard intermittently in the region of the junction of the fourth interspace and sternum. The lungs demonstrated only scattered rhonchi on auscultation. Oxygen, which had been discontinued the day before, was reinstituted. The first electrocardiogram (Fig. 3) taken at this time revealed a rate of 82 per minute, with sinus rhythm. There was notching of the upstroke of the R wave in Lead AVF, depression of the ST segments in Leads V_3, V_4 and V_5 and coved inversion of the T waves in Leads 1, 2, 3,

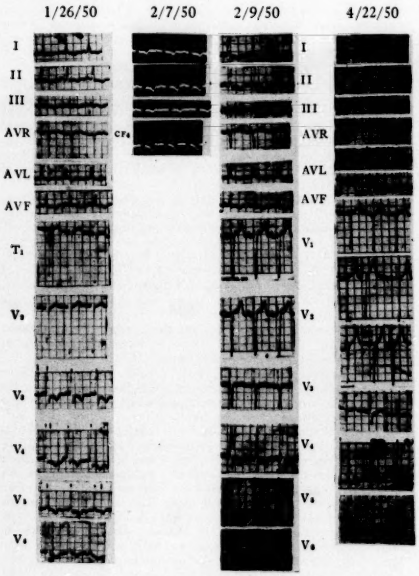

FIGURE 3. *Serial Electrocardiograms in Case 2.*

AVF, V_3, V_4, V_5 and V_6; the T wave in Lead AVR was upright. An x-ray film of the chest taken on the following morning showed increased bronchovascular markings; no evidence of mediastinal emphysema or pneumothorax was visible radiographically, although a lateral film was not obtained. Minimal subcutaneous crepitation remained in the supraclavicular fossae for 2 days, but the rub-like sound heard over the sternum disappeared on the morning after its discovery. Substernal hyperresonance was noticeably decreased, and the heart tones were of increased intensity on January 28. The urinary urobilinogen, which had been absent on admission, was present in 1:80 dilution on January 28, returning to normal on January 31. The sedimentation rate was 35 mm. per hour and remained elevated throughout the hospital course. The icteric index was 9, and the nonprotein nitrogen 57 mg. per 100 cc. A repeat x-ray film of the chest on February 8 showed the heart and lungs to be within normal limits. Serial electrocardiograms revealed progression of T-wave inversions, indicative of posterior infarction with anterolateral extension.

On bed rest and mercurial diuretics recovery was uneventful. After discharge to the Cardiac Clinic the patient remained well with the exception of some shortness of breath on exertion. A follow-up electrocardiogram on April 22, 1950, showed that the T wave in Lead 2 had become diphasic; the T waves were upright in Leads 3 and V_4, isoelectric in Lead AVF and inverted in Leads 1, V_5 and V_6.

Discussion

Although several authors have referred to the possible effects of mediastinal emphysema on coronary blood flow, no cases have been reported in which spontaneous mediastinal emphysema was associated with myocardial infarction. It is interesting that since Hamman's first report, which included 3 cases of spontaneous mediastinal emphysema simulating myocardial infarction, the primary differential diagnosis has continued to involve these two entities in practically all cases. It is the purpose of this paper to point out that the two conditions may occur simultaneously, in which event there is quite possibly an etiologic relation.

Experimentally, Macklin[3] has conclusively demonstrated the pathogenesis of spontaneous mediastinal emphysema and its resultant pathologic effects on the cardiovascular system. He has shown in animals that increasing the intra-alveolar pressure leads to minute ruptures in the bases of the alveoli with the passage of air into the underlying vascular sheaths of the pulmonic capillaries. In overdistending the lung, alveoli pull away from the capillaries, producing a pressure gradient that decreases toward the vascular sheaths. This negative gradient toward the vessel is also enhanced by conditions that diminish the blood volume in pulmonary vessels and thus decrease their circumferential area. Once air has gained access to the vascular sheaths underlying the alveoli, it dissects medially in these sheaths, exerting a compression effect on the vessels, both arterial and venous. Macklin believes that the lengthening and shortening movements of the pulmonic vessels associated with similar movement of the bronchi in respiration cause the bubbles of air, gradually increasing in size, to move along the vascular sheaths. Once arrived at the root of the vessels in the hilus, blebs form, exerting an even more widespread obstructive vascular effect that markedly impedes pulmonary circulation and leads to subsequent right-sided heart failure. He observed that the vessels were infrequently "completely encroached on by the bubbles and in extreme cases the circulation was stopped."[3] Thus, dissection of the air was found to follow along the vascular sheaths to the hilus of the lung and on into the mediastinum, which became distended, and with continued insufflation, overflowed into the anterior mediastinum, retroperitoneum and subcutaneous tissues of the neck and axillas. Extreme distention ruptured the mediastinal wall, leading to pneumothorax.

Macklin has thus shown that mediastinal emphysema originates in pulmonic interstial emphysema, both of which lead to significant circulatory embarrassment by virtue of external vascular compression. Ballon and Francis,[4] studying the effects of air injected into the mediastinum of rabbits, noted decreased heart action, pooling of blood in the lungs, pulmonary edema and development of fluid in the pericardial cavity. Injections of air into the mediastinum experimentally have been shown not only to compress the systemic and pulmonic veins, thus obstructing the return flow of blood to the right and left auricles respectively, but also to restrict contractions of the heart as a pericardial effusion would.[5] Macklin[3] concludes further from his experiments dealing with mediastinal emphysema that the "coronary vessels must be compressed in marked cases and it seems likely that the flow within them is slowed." Jessup,[6] discussing the pathology of mediastinal emphysema states: "The outstanding effect is a mechanical interference to circulation brought about by compression of the large veins entering both sides of the heart."

Although study of the effect of pneumomediastinum in human subjects has been limited, some of the pathologic features produced experimentally have been verified clinically. Macklin[3] has noted the air-tunneled vascular sheaths in human beings, similar to that seen in his animal experiments. Jehn and Nissen[7] describe a case of mediastinal emphysema in which the heart was so greatly compressed that it contained no blood; the arteries and veins of the mediastinum were collapsed, and only the large systemic veins of the body and pulmonic veins within the lungs were dilated with dark blood. Torrey and Grosh,[8] reporting their cases in which mediastinal emphysema was present, stated that ". . . marked stasis of all veins entering the chest and those drained by the superior vena cava was manifest." Again, Hamman[9] cites Sauerbruch as finding at operation on a man with mediastinal emphysema that the mediastinum was greatly blown up, with resulting marked engorgement of the vena cava and azygos veins. Acute pulmonary edema associated with pneumomediastinum has been described.[10] Fisher[11] reported a case of spontaneous pulmonic interstitial and mediastinal emphysema in an infant that, at autopsy, demonstrated the exact changes noted experimentally by Macklin — namely, accumulations of bubbles of air in the perivascular sheaths that compressed the pulmonary vessels ". . . to such an extent as to seriously impede blood flow through them." There was slight dilatation of the right atrium and the right ventricle. Acute strain of the right ventricle associated with spontaneous mediastinal emphysema has also been reported.[12]

McCabe[13] believes that interstitial emphysema compresses the pulmonary venous system, leading to right-sided heart stasis, which secondarily embarrasses return from the cardiac thebesian veins and coronary sinus. Miller[14] likewise suggests the occurrence of a functional coronary insufficiency on the same basis and also believes that a direct pressure effect on the coronary vessels is possible, as is a tamponade effect on the heart itself.

It appears from the foregoing that an etiologic relation between mediastinal emphysema and myocardial infarction might be justifiably postulated. The circulatory embarrassment brought on by extravascular compression of the systemic and pulmonary veins, as well as a possible compression effect on the heart itself, may have serious consequences. It is not improbable that the combined effects of decreased cardiac output, pulmonary stasis and possible slowing of the coronary blood flow lead to myocardial ischemia and infarction, with or without coronary occlusion.

Summary

Spontaneous mediastinal emphysema occurring in an older patient and particularly in the presence of cardiac disease bears a serious prognosis. Not only must spontaneous mediastinal emphysema be differentiated from myocardial infarction, but also the possibility of their coexistence must be considered. Experimental and clinical studies are cited to provide a theoretical basis for a causal relation between the two conditions.

Two cases are presented in which spontaneous mediastinal emphysema was complicated by acute myocardial infarction.

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EFFECT OF AUREOMYCIN ON THE DEVELOPMENT OF COLD AGGLUTININS IN PRIMARY ATYPICAL PNEUMONIA*

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THE favorable influence of aureomycin on the course of primary atypical pneumonia has raised the question whether this antibiotic affects the development of cold agglutinins. The characteristic variation in severity and duration of this disease and the frequent disparity between its initial symptoms and its clinical and roentgenographic findings[1] make it difficult to evaluate the effect of a therapeutic agent and to compare treated and control groups. These obstacles to valid comparisons between groups of patients are less troublesome when a study can be made in a boarding school or military setting. In either of these situations subjects must either report for all their day's duties or report for medical care, a fact that makes it likely that all cases of this illness developing in the community will be seen by its medical service and that they will be seen shortly after the onset of disease.

This report is concerned with a comparison of titers of cold agglutinins in a consecutive series of cases of primary atypical pneumonia that developed at a boys' boarding school. Alternately, the patients either were given aureomycin or received no antibiotic. Cold agglutinins are known to increase during the course of this disease,[2-4] but their relation to immunity and their validity as an index of it are still matters for speculation. Brainerd et al.[5] have stated that aureomycin may interfere with the development of complement-fixing antibodies in psittacosis. The present study was undertaken as a preliminary attempt to investigate the effects of antibiotics in primary atypical pneumonia; some reduction in cold-agglutinin titers in patients treated with aureomycin was indicated from the study of Meiklejohn and Shragg.[6]

MATERIAL

From January to April, 1950, all students who were admitted with fever and cough to a hospital attached to a boys' boarding school were immediately selected as possible candidates for this study. Clinical histories, chest roentgenograms, blood counts and physical examinations were done within a few hours of admission; on the basis of these findings, and whenever possible, within thirty-six hours after admission, the decision was made regarding whether primary atypical pneumonia was present, and the patient was assigned by the alternate case method either to the group to be treated with aureomycin or to the group that was to receive no specific therapy.

Aureomycin was given in doses of 250 mg. every three hours (eight times a day); it was continued for three days (twenty-four doses) after the time when the temperature first fell to and subsequently stayed below 99.4°F. Patients in the untreated group received no medication other than rest in bed and an occasional dose of codeine. Blood was taken for cold-agglutinin tests during the first week, and on about the eighth, fifteenth and twenty-second day after admission; in most cases a fifth sample was obtained about three months after the admission date. The 16 cases of primary atypical pneumonia that occurred during those months developed in boys ranging in age from fifteen to eighteen years. Chest roentgenograms were taken shortly after admission and on every day thereafter until the lung fields were clear.

The time of onset of this illness is often difficult to determine. However, since only 1 of our patients was admitted more than forty-eight hours after the onset of malaise and since 9 were admitted twelve hours after even the slightest symptom was first apparent, the day of admission has been arbitrarily designated as the first day of illness.

TECHNIC OF COLD-AGGLUTININ TEST

Blood obtained for cold-agglutinin tests was kept in an incubator at 37°C. until it clotted. It was then ringed and centrifuged, and the separated serum stored under aseptic conditions in a rubber-capped bottle in a refrigerator. Cold-agglutinin tests were deferred until the first four samples of each patient's blood were available so that the same suspension of red cells could be used throughout. Serum dilutions of 1:4 through 1:8192 were made in isotonic saline solution.

To the dilutions of the patients' serum (1.0 cc. in each tube) 0.1 cc. of a 2 per cent suspension of washed human Group O red cells was added. These tubes were kept overnight at a temperature of 0 to 5°C. The red-cell suspension was obtained in the following manner. To a tube containing 0.6 cc. of a 3 per cent solution of sodium citrate in saline, 5.4 cc. of International Group O blood was added. After centrifugation at low speed the supernatant fluid was withdrawn, 5.0 cc. of isotonic saline solution added, and the suspension again centrifuged. Washing was repeated two or three times until the supernatant fluid was clear. A 2 per cent suspension of

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red cells was made by the addition of 0.2 cc. of washed cells to 9.8 cc. of isotonic saline solution.

Readings were made on the following morning directly after the tubes were taken from the refrigerator. When many tubes were to be read, they were placed on a tray of ice cubes so that their temperature would remain fairly constant. The tubes were not shaken; prior to a reading they were gently inverted two or three times. A ± reading indicated loss of whirl only; + indicated granulation but the retention of a red coloring in the background; ++ indicated more definite granulation and only slight redness in the background; +++ indicated that the agglutination occurred in large particles, the fluid remaining very clear; and a ++++ rating was given when the red cells remained in a solid disk and the background was colorless. A hand lens was necessary to making readings less than ++. Tables 1 and 2 show the readings in serums of an untreated and in an aureomycin-treated patient, respectively. The titers were recorded as the dilution showing at least + agglutination.

TABLE 1. *Dilutions in Which Cold Agglutinins Were Present in the Serum of a Patient Who Was not Given Antibiotic Therapy.*

Serum Dilution	Titer on Respective Day of Disease				
	5th day	12th day	19th day	26th day	89th day
1:4	+	++++	++++	++++	+++
1:8	±	++++	++++	++++	++
1:16	±	++++	++++	++++	+
1:32	0	++++	++++	++++	+
1:64	0	++++	+++	++++	+
1:128	0	+++	+++	+++	0
1:256	0	+++	+++	+	0
1:512	0	++	+	±	0
1:1024	0	+	±	0	0
1:2048	0	±	±	0	0
1:4096	0	0	0	0	0
1:8192	0	0	0	0	0

All serums were tested for cold agglutinins by the above technic and also by a similar method utilizing a much heavier suspension of red cells. Since the results of the two technics were almost identical and readings in the second method more difficult to make, that technic is not described.

TABLE 2. *Dilutions in Which Cold Agglutinins Were Present in the Serum of a Patient Who Was Given Antibiotic Therapy.*

Serum Dilution	Titer on Respective Day of Disease				
	5th day	12th day	19th day	26th day	89th day
1:4	0	+++	++	++	0
1:8	0	+++	+++	+	0
1:16	0	+++	+++	+	0
1:32	0	+++	++	0	0
1:64	0	++	+	0	0
1:128	0	+	0	0	0
1:256	0	±	0	0	0
1:512	0	0	0	0	0
1:1024	0	0	0	0	0
1:2048	0	0	0	0	0
1:4096	0	0	0	0	0
1:8192	0	0	0	0	0

Results

In 14 of the 16 cases a determination of the cold-agglutinin titer was made before the seventh day after admission to the hospital, and in only 2 of these 14 cases was the reading positive in as high a dilution as 1:32. One patient in the untreated group whose serum was not tested until the seventh day was then found to have a serum cold-agglutinin titer of 1:128. Another, a member of the treated group, was not tested until the ninth day, when the serum was positive in the 1:16 dilution. Five of the untreated group showed cold agglutinins in no higher than a 1:4 dilution during the first six days of illness, as did 6 members of the group subsequently treated with aureomycin.

However, serums tested between the fourteenth and nineteenth days of the disease demonstrated a considerable difference between the two groups. Six of the untreated patients showed cold agglutinins in titers ranging from 1:256 to 1:2048. At that same period only 1 of the patients who had received aureomycin showed a titer as high as 1:256, and 3 had titers no higher than 1:32. All members of the untreated group were again tested between the twentieth and the twenty-sixth day of illness, and during that interval 4 were found to have titers of 1:256 or higher; only 1 had a titer as low as 1:32. In the treated group, on the other hand, during the same interval, only 2 of the 7 tested showed cold agglutinins as high as the 1:128 dilution, and the 5 others had titers of 1:32 or less.

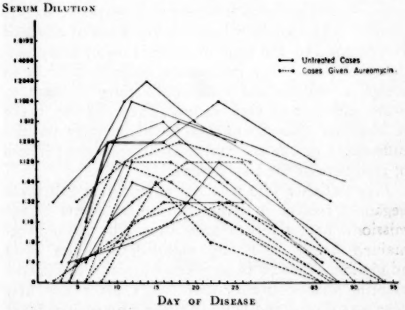

FIGURE 1. *Graphic Comparison of the Heights and Duration of Cold-Agglutinin Titers in Patients Given Aureomycin with Those Given No Antibiotic.*

Serum from 6 of the untreated and from 7 of the treated patients was obtained about three months after the onset of illness. Three of the untreated patients showed a positive cold-agglutinin titer in the 1:32 dilution or higher at this time, whereas a positive agglutinin test was observed in only 1 of the treated patients, and then only in the 1:4 dilution.

Tables 1 and 2 present the details of the cold-agglutinin tests on one member of each of the two groups and indicate the degree to which the tests were positive on successive days. Figure 1 clearly indicates that the cold-agglutinin titers rose more rapidly and achieved and sustained higher levels for a longer time in the untreated patients than in those who received aureomycin.

Discussion

It is well known that this disease varies considerably in severity and duration, and although the alternate case method was used and there is no reason to believe that the cases were unevenly distributed in severity, their number is too small to allow more than observations on the differences between the treated and the untreated patients. In spite of the fact that the patients usually came under observation shortly after the onset of symptoms, such factors as differences in response to discomfort and variation between the time of onset of symptoms and the time of appearance of x-ray evidence of pulmonary infiltration make it difficult to assign a definite and comparable time of onset to every member of each series. These factors make it essential that comments be made only on the differences in clinical course and duration of illness of members of the two groups.

Five patients who received aureomycin (all these began to receive it within forty-eight hours of admission) had temperatures that fell to and remained below 99°F. by eighty-four hours after admission. Two of those given aureomycin became afebrile within twenty-four hours after the first dose was given, and none of those treated had fever forty-eight hours after the initial dose. Only one member of the untreated group had fever that did not last longer than this, and his was an extraordinarily mild illness with only minimal x-ray findings. The other members of the untreated group had fever for five to eight days. The interval between the first positive x-ray findings and the clearing of the pathologic process was also shorter in the treated group, the average being about seven days whereas that for the untreated group was about eleven days.

These comments on the clinical and x-ray findings have been made more with the intention of describing the groups upon which the cold-agglutinin tests were made than for the purpose of evaluating the effect of aureomycin upon this illness. Most workers are agreed that aureomycin has a salutary effect on the course of primary atypical pneumonia[7]; however, it seems worth while to review some of the difficulties involved in the evaluation of the effect of any agent upon this disease. It should be emphasized that this illness often appears in a mild form and that, even when x-ray findings are extensive, patients given no further treatment than bed rest frequently make a rapid and satisfactory recovery. One of our untreated patients who was admitted with x-ray findings typical of the onset of the disease had fever for only three days, and x-ray films of the lungs were completely clear in nine days; this was a mild illness with minimal x-ray findings. Another untreated patient, whose initial x-ray film showed involvement of the entire right lower lobe, had a completely clear film eight days later.

Aureomycin or other antibiotics effective in the treatment of primary atypical pneumonia should undoubtedly be used when the infection is severe or the patient debilitated. Whether or not the cold-agglutinin titer has a relation to a patient's antibody response or to his degree of immunity to subsequent infection by the causative agent of this disease, it seems proper to question the routine use of specific treatment. This appears particularly worthy of consideration because this illness frequently runs a mild and brief course and because a positive diagnosis occasionally cannot be made until as late as the fourth or fifth day (this was true in 4 of our 16 cases), when the febrile course of the disease has little longer to run. A development of immunity against subsequent attacks of this or other illnesses and the occasional stimulation of a person's own protective mechanism are matters that may deserve more consideration than is at present always given them. Desirable as it may often be to abort an attack of illness quickly and dramatically, it may more than occasionally be wise to evaluate the price of a cure that may provide little opportunity for the patient to utilize or develop his own protective mechanism.

Summary

Cold-agglutinin titers and some clinical observations are presented on two groups of patients with primary atypical pneumonia. One group was treated with aureomycin, and the other was given no treatment but bed rest. Each group was made up of 8 previously healthy boys ranging in age from fifteen to eighteen years.

Patients who were not given aureomycin developed higher titers of cold agglutinins and sustained them longer than those who were treated with this antibiotic.

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ANTIMICROBIAL TREATMENT FOR VIRAL AND RELATED INFECTIONS*

I. Antibiotic Treatment of Primary Atypical Pneumonia

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BEFORE the introduction of aureomycin it was generally conceded that the so-called primary atypical or "viral" pneumonias were not benefited by the available antimicrobial agents.[1] Indeed, the failure of a patient with an acute pulmonary infection to respond favorably to treatment with sulfonamides and penicillin was often accepted as one of the major criteria for the diagnosis of primary atypical pneumonia, provided that evidence for the presence of a definite inciting cause or agent could not be demonstrated. With the establishment of effectiveness of aureomycin and chloramphenicol against rickettsial infections and against infections with organisms of the psittacosis-lymphogranuloma-venereum-trachoma group,[2, 3] it was natural to explore the possible effectiveness of these antibiotics in primary atypical pneumonia because: nonbacterial pneumonias caused by micro-organisms of these general groups have been well recognized[4]; the isolation, identification, cultivation and transmission to laboratory animals of some of these agents is difficult or not possible; the exact nature of the etiologic agent or agents of primary atypical pneumonia is not known and could conceivably be related to one or another of these groups of micro-organisms; and the clinical and pathologic manifestations of primary atypical pneumonia may be indistinguishable from the pneumonias caused by micro-organisms of the groups mentioned, as well as by other nonbacterial (viral) agents.[4]

CLINICAL RESULTS WITH AUREOMYCIN

The first reports dealt with the use of aureomycin orally[5-7]; they seemed to indicate quite clearly that pneumonias satisfying the accepted criteria for the diagnosis of primary atypical pneumonia, in which known etiologic agents were excluded as far as feasible and most of which had failed to improve under treatment with penicillin or sulfonamides, or both, did respond with great regularity to oral treatment with aureomycin by defervescence and marked symptomatic improvement, usually within two days or less of the first dose. These first reports noted such favorable responses in 53 consecutive adult patients in three different clinics, and additional observations by the same three groups of workers[8-10] soon increased to nearly 100 the number of consecutive patients in almost all of whom similar effects were elicited. In each case, these observers had had previous experience with the variable and unpredictable course of this disease, which they either referred to or presented in some detail; however, direct comparisons with similar cases observed concurrently along with deliberately planned controls selected at random and not treated with aureomycin were not included with any of these three series.

A number of additional reports showing equally favorable effects from aureomycin in small numbers of cases of primary atypical pneumonia have appeared.[11-29] Most of them included cases that were not so intensively studied; some of the reports dealt with atypical pneumonias along with other acute respiratory infections,[14, 15] and others included such cases as part of general surveys of the clinical effectiveness of aureomycin in various infections[11, 13, 22, 27] or merely mentioned that their results in atypical pneumonias were favorable.[18, 19] Most of the reports dealt with cases in adults, but some were concerned with infants and children.[15-19] The favorable responses in adults were generally obtained with daily doses of 2 to 6 gm. per day (0.5 or 1.0 gm. every four or six hours); however, in one study of 14 patients, the results obtained with doses of 1.0 or 1.5 gm. per day (0.25 gm. every four or six hours) were considered to be equally favorable, more acceptable, less troublesome and yet not associated with relapses during the course of treatment.[20] Therapy has usually been continued for two to four days after the patients became afebrile and were symptomatically improved. Early discontinuance of treatment was followed by relapse in occasional patients; most of these relapses, however, seemed again to respond favorably when treatment with aureomycin was resumed.

CLINICAL RESULTS WITH OTHER ANTIBIOTICS

Soon after the publication of the early observations dealing with aureomycin, there appeared other reports of similar results in small numbers of cases of primary atypical pneumonia treated with chloramphenicol.[13, 30-34] Later, when terramycin was made available, equally favorable effects were obtained with this agent.[35-39] As already noted

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penicillin and the sulfonamides are generally conceded to be without any beneficial effect on the course of primary atypical pneumonia. Regarding streptomycin, however, very little in the way of recorded data are available. Keefer and Hewitt's[40] compilation of 3000 cases treated with streptomycin includes only 2 cases of primary atypical pneumonia, and it is merely noted that this antibiotic was without effect. One patient with this disease is included in the report by Pulaski and White[41] on the clinical effects of streptomycin in various respiratory-tract infections; the result in this case is listed as poor. Two patients in whom streptomycin might be considered as having had a favorable influence on the course of this disease were presented by Finland et al.,[7] but in these cases the beneficial effects were not so striking as in the patients treated with aureomycin. Bickel and Plattner[39] reported 4 cases of particularly severe primary atypical pneumonia in which penicillin alone and then penicillin in addition to streptomycin failed, but institution of therapy with terramycin, 3 gm. daily, gave excellent results. King,[42] however, reported definitely favorable results from streptomycin in 10 patients, in 5 of whom the disease was mild; in the other 5 it was moderately severe. In each of his cases the patient failed to improve during several days of observation under treatment with penicillin, but the fever subsided and symptoms improved promptly, in most of them about twenty-four hours after streptomycin therapy was started. The lesions in the lungs of these patients were said to have cleared in normal fashion. Clearing of pulmonary lesions in aureomycin-treated patients has been noted as occurring somewhat more rapidly than in untreated controls or in penicillin-treated patients, but this feature has not been uniform or striking and has been rather difficult to measure properly.

Controlled Clinical Studies

In addition to the reports already referred to and similar ones in which there were no controls deliberately planned or randomized there are a few studies in which attempts were made to compare the results in concurrent patients treated with different agents or receiving no antibiotic. Because of the marked variability in the febrile course, symptomatology, pulmonary findings and serologic results in cases of primary atypical pneumonia, these "controlled" studies are worthy of special attention.

The Fort Ord Study

The first of these was that conducted by Meiklejohn and Shragg[43] at the Station Hospital, Fort Ord, California. They included in their study only patients who satisfied the following criteria: the clinical course and physical findings were characteristic of primary atypical pneumonia; the roentgenograms showed unequivocal evidence of pneumonia; the patient's temperature was 102°F. or higher during the twenty-four hours before treatment was started; the white-cell count was less than 12,750; and the patient did not appear to be showing significant improvement. Adherence to these criteria necessitated the exclusion of more than half the patients whose course suggested that of primary atypical pneumonia and left in the study cases of at least moderate severity that offered a better opportunity to compare the results of the test therapy.

Alternation was accomplished in 30 patients who met the criteria outlined; half of them received penicillin and the others received aureomycin, each according to a strict and predetermined schedule. During the same period 5 patients who received penicillin and 3 who were given aureomycin shortly after admission were subsequently found to meet all the criteria for inclusion in the study and were later included in the analysis, the choice of their therapy having been made at random. Analysis of the cases according to age, duration and height of fever, admission leukocyte count and roentgenographic findings showed no significant difference between the two groups and confirmed the random character of the selection.

The dose of penicillin was 100,000 units intramuscularly every six hours. Aureomycin was given by mouth, 1.0 gm. every six hours, with an intravenous dose of 50 mg. before the first oral dose and 100 mg. before some other oral doses in patients who did not tolerate the drug well by mouth. In 4 of the penicillin-treated patients, because the condition became worse and was moderately alarming after forty-eight hours, aureomycin was later substituted and was followed by prompt improvement. Treatment was usually continued for more than two days after symptomatic improvement had occurred.

Analysis of the results of treatment indicated that whereas a third of the patients treated with penicillin recovered within forty-eight hours, the course in the remaining two thirds showed that this agent had no effect; the majority remained febrile for three days or more, and 7 of the 20 patients had fever for more than five days after penicillin therapy was started. In contrast, all patients receiving aureomycin showed definite symptomatic improvement within three days, two thirds of the patients became afebrile within forty-eight hours, and none had fever for more than five days. It was the impression of the attending physicians that clearing of the physical signs and roentgenographic findings in the chest was more rapid in the aureomycin-treated patients, although this lagged behind the symptomatic improvement.

In 3 of the aureomycin-treated patients, there was a recurrence of low-grade fever and of pulmonary infiltration several days after treatment was stopped. Two of these patients, who also had leukocytosis, were then treated with penicillin without effect, but substitution of aureomycin resulted in prompt

improvement; the third patient improved twenty-four hours after retreatment with aureomycin was started. Reactivation or extension of the disease was not noted during the course of aureomycin treatment in any case. Similar relapses following cessation of aureomycin or chloramphenicol therapy have also been noted in rickettsial infection both in man and in laboratory animals.[44-46]

The results of tests for cold hemagglutinins in the two groups of patients were also of interest. Significant titers (32 or more) were demonstrated in 12 of the 20 patients who were treated with penicillin, and in 5 of them the titer was 128 or more; by contrast only 6 of the 18 who received aureomycin had a significant titer, which in only 1 case was more than 64. As was to be expected from previous observations,[47] the significant titers were most frequent in the patients who had the longest febrile course.

On the basis of the prompt therapeutic response observed in the 22 patients with primary atypical pneumonia who were treated with aureomycin, the definite variation in the duration of the disease in the control group of 20 patients who were treated with penicillin and the comparison of the duration of fever in these 2 groups of patients, Meiklejohn and Shragg[48] concluded that penicillin is not an effective drug and that aureomycin is highly effective in primary atypical pneumonia. These authors also suggested that the treatment with aureomycin probably suppressed the formation of cold hemagglutinins.

The Johns Hopkins Hospital Series

The report of the clinical experiences with aureomycin at the Johns Hopkins Hospital[48] included 6 patients with primary atypical pneumonia who were treated with this antibiotic and 9 additional patients with the disease who were admitted to the hospital during the same period and received no chemotherapy. Five of the latter were alternate admissions to the 6 who received aureomycin; the average total dose was 13.3 gm. given over an average of eight and a half days. All 6 of the aureomycin-treated patients developed agglutinins against streptococcus MG, but only 1 of them developed cold hemagglutinins; of the 5 alternated untreated patients, 4 who were tested developed agglutinins for streptococcus MG, and none developed cold hemagglutinins.

Among the aureomycin-treated patients the temperature reached normal on the sixth to the seventeenth day (average, eleven days) of the disease; this was four to seven (average, five and a half) days after admission to the hospital and from two to five (average, four) days after treatment with aureomycin was begun. Among the 5 alternated patients who were treated without chemotherapy, the temperature reached normal on the fourth to the eighteenth day (average, eight and eight tenths) of the disease and only one to four (average, two and two tenths) days after admission to the hospital. The other 4 untreated patients were febrile until the seventh to the seventeenth day (average, twelve and eight-tenths days) of the disease and from three to nine (average, five and three tenths) days in the hospital. According to the authors, the results in this small group of patients failed to indicate that aureomycin in the dosage used affected the course of this disease; they suggested that larger groups of patients with adequate controls are necessary to settle this point.

However, since these results have been cited as strong evidence that aureomycin is ineffective in primary atypical pneumonia, the following features of the data presented are worth noting: the low incidence of cold hemagglutinins (1 in 12 patients tested) is unusual, particularly in view of the fact that the temperature did not reach normal until the ninth day or later in all but 1 of the negative cases; the temperature reached normal in 3 of the 5 alternate controls who received no chemotherapy in one or two days after admission to the hospital, and aureomycin was not begun in 4 of the 6 patients until they had been in the hospital for one to four days; and in only 1 of the 6 patients did the temperature reach normal two days after aureomycin therapy was started — in the other 5, fever continued during four or five days of aureomycin therapy. This is the reverse of the findings of all the other studies cited above, in which fever lasting more than three days after aureomycin treatment was started was rarely encountered. A ready explanation for these discrepancies is not evident from the data presented, but the findings suggest that there was a different disease in most of these patients, that there was an unconscious selection either of mild cases for the control group to receive no chemotherapy or of unusually severe or otherwise unfavorable cases for treatment with aureomycin, or that the aureomycin used in these cases was inactive or was not administered in an optimum manner.

Danish Series

In a third study, Hilden and Nørregaard[49] reported 13 cases of primary atypical pneumonia treated with aureomycin and 12 control cases. The diagnosis was made from the clinical picture and confirmed by the failure of the patients to respond to penicillin and sulfonamide treatment. In 12 of the 13 patients the temperature became normal in one to three days after aureomycin was started whereas the response of the control patients was irregular and more prolonged. The dose of aureomycin used was 0.5 gm. by mouth five times a day.

Lackland Air Base Study

A fourth report of "controlled studies" on the use of aureomycin, chloramphenicol, streptomycin and

penicillin in 141 "unselected" cases of primary atypical pneumonia observed at Lackland Air Force Base was presented by Peck and Berry.[50] Their patients were almost all newly inducted recruits with an average of seven weeks and a maximum of three months of military service. All had acute respiratory disease with symptoms averaging four days in duration before admission and some pulmonary infiltration demonstrated by x-ray examination at the time of entry. Other known etiologic agents were excluded by bacteriologic studies and serologic tests. Only the finding of significant titers of cold agglutinins, the duration of fever and the number of days required for the lungs to clear by x-ray examination were compared.

Two series of cases were studied. An initial control series, which was observed between February 20 and April 20, 1949, consisted of 31 patients who received 50,000 units of penicillin intramuscularly every three hours and a symptomatically treated group of 15 patients. Among these 46 cases, cold hemagglutinins were demonstrated in 59 per cent, the average duration of fever was five and three-tenths days and x-ray clearing of the lungs occurred in an average of fourteen days. The results in the penicillin-treated patients and in the symptomatic groups were similar except that fever subsided sooner without penicillin (average of three and a half days) than in those receiving this agent (average of six and one-tenth days). The frequency with which rapid or delayed defervescence occurred in the two groups, however, was not stated.

The second series in this report consisted of 95 patients hospitalized for primary atypical pneumonia between April 21 and June 20, 1949. These were divided into five groups as follows: 24 who were treated symptomatically; 21 who received penicillin as in the first series; 25 who were given chloramphenicol, beginning with a loading dose of 1.5 gm. and then either 25 or 50 mg. per kilogram of body weight daily in divided doses at intervals of four or six hours until the temperature remained normal for seventy-two hours; 17 who received aureomycin in the same dosage as for chloramphenicol; and 8 who received streptomycin, 2.0 gm. in the first twenty-four hours and 0.25 gm. every six hours thereafter. The streptomycin series was started late and aureomycin was not available for part of the study; otherwise the types of therapy were rotated among the patients at the time of admission to the hospital.

The authors found it quite difficult to interpret the clinical response in these cases because the majority of the patients did not feel ill enough at the onset of therapy to be expected to manifest any dramatic or striking improvement. In the second series, cold hemagglutinins were demonstrated in only 16 per cent of all the cases, varying from 6 and 9 per cent in the patients treated with aureomycin and symptomatically, respectively, to 34 per cent in those treated with penicillin. Only the average of the duration of fever was given for the various therapeutic groups; this was, respectively, four and six-tenths, two and eight-tenths, two and six-tenths, one and six-tenths and one and four-tenths days in the group given penicillin, symptomatic treatment, chloramphenicol, aureomycin and streptomycin respectively. The frequency with which rapid or delayed defervescence occurred in the different groups was not reported. Clearing of the lungs on x-ray examination occurred after an average of eighteen and a half days in the penicillin-treated cases and after an average of nine and four-tenths to twelve and a half days in the other groups. Here again, the frequency of rapid or delayed clearing in the individual groups was not given. The possibility that a small number of cases with unusually long durations of fever or pulmonary infiltrates vitiated the value of the averages is therefore not excluded.

A comparison of the percentage of patients with positive cold-agglutinin titers in the early and late series suggested to the observers that some kind of change occurred in the invading agent. In the second series, three fourths of all the patients were considered to have a mild disease when first seen, and only 3 were rated as having a disease of more than moderate severity. Peck and Berry concluded that their data showed that none of the antibiotics, as employed by them, produced any reduction in the noneffective rate resulting from the milder forms of primary atypical pneumonia.

It should be noted, however, that cases of the type included in the second series are almost impossible to differentiate from minor respiratory illnesses that may be associated with transient radiographic shadows.[51] Moreover, the high incidence of simple acute respiratory infections in new recruits during the first few weeks after they enter training has now been well demonstrated.[52] It is therefore difficult to draw any conclusions from these results regarding the efficacy of these forms of treatment in the types of cases studied by other workers, the majority of them being at least of moderate severity, or even regarding the possible effect of the same agents in the types of cases observed by the same authors in their first control series. Even so, it is of interest that the shortest average duration of fever and of radiographic signs in the lungs appeared to be in the group of patients who were treated with aureomycin; also, in view of the findings of Meiklejohn and Shragg,[43] it is worth noting that the lowest incidence of positive cold-agglutinin titers was observed in the same group.

Comparison of Various Antibiotics in Infants and Children

The report by Graves and Ball[53] on the evaluation of the treatment of primary atypical pneumonia

in infants and children with aureomycin, chloramphenicol and terramycin may be mentioned briefly. They treated 58 patients with aureomycin, 66 with chloramphenicol and 19 (as well as 17 additional cases noted in proof) with terramycin; more than one fifth of these patients were afebrile throughout. Alternation between the first two and later between all three antibiotics was carried out for part of the study. The disease was noted as particularly severe in infants under one year of age, and they were treated without alternation after the first few weeks. In 6 older children who were observed during the same period without antibiotic treatment the average duration of fever was six and a half, and the range three to fourteen days; symptoms continued for an average of twenty-six days, and roentgenographic findings in the lungs for an additional one to four weeks. The results of therapy with the different agents were considered to be excellent or good in 90 to 94 per cent of the cases, and relapses after treatment were noted in a total of only 5 patients. Although the data indicated no significant difference between the results obtained with the three antibiotics the authors obtained the clinical impression that terramycin was the drug of choice.

Chang[54] reported a series of 42 cases with characteristic findings of primary atypical pneumonia associated with significant titers of cold agglutinins in 88 per cent. Five of these patients were treated with aureomycin; 4 of them had previously failed to benefit from other antibiotics, and all improved after aureomycin therapy was started. Three of these patients were afebrile within twenty-eight hours, 1 within forty hours and the fifth in sixty hours after the first dose of aureomycin. The average duration of fever and symptoms was thirty-six hours in the aureomycin-treated patients as compared with an average febrile course of four and eight-tenths days after admission in patients not receiving aureomycin.

Controlled Study on Effect of Aureomycin on Cold-Agglutinin Titers

Finally, a study by Gallagher and Gallagher[55] of 16 consecutive cases of primary atypical pneumonia in schoolboys fifteen to eighteen years old is of particular interest. This study was carried out primarily for the purpose of evaluating the effect of aureomycin therapy on the development of cold hemagglutinins. A clinical history was obtained, and physical examination, chest roentgenograms and blood counts were done in each patient within a few hours of admission to the hospital. As far as possible, a decision whether primary atypical pneumonia was present was made within thirty-six hours, and the patients were then assigned alternately to the group to be treated with aureomycin or to the group to receive no chemotherapy. Aureomycin was given by mouth in doses of 250 mg. every three hours until the temperature remained below 99.4°F. for three days. No medication other than an occasional dose of codeine was given to the alternate control patients. Blood samples were obtained during the first week, again on about the eighth, fifteenth and twenty-second days and after about three months. X-ray examinations of the chest were repeated frequently until the lungs were clear. Only 1 of the patients was admitted more than forty-eight hours after the onset of malaise, whereas 9 were admitted within twelve hours of their first symptom.

A rise in titer of cold hemagglutinins was demonstrated in every one of these 16 patients. There was a distinct difference, however, between the results in the two groups. The cold hemagglutinins appeared sooner, the titers rose more rapidly, maximum titers were attained earlier and elevated titers were sustained longer in the 8 patients who received no antibiotic as compared with the titers found in the 8 patients who were treated with aureomycin.

Although this study was not specifically intended as an evaluation of the therapeutic effect of aureomycin, the difference in the clinical course of the two groups is worth noting. Whereas 5 of the 8 aureomycin-treated patients became afebrile within eighty-four hours after admission, only 1 of the untreated group, "a patient with an extraordinarily mild illness," became afebrile within the same period. All the other 7 untreated patients had fever for from five to eight days in the hospital. Aureomycin treatment was begun in every instance within forty-eight hours after admission; 2 of the patients became afebrile within twenty-four hours after the first dose, and none had fever more than forty-eight hours after aureomycin was started. The interval between the first positive x-ray findings and the clearing of the pathologic process was also shorter in the aureomycin-treated group, the average for the latter being about seven days whereas for the untreated group it was about eleven days.

Critique of Controlled Studies

It is evident from the various clinical reports that have been cited that not all the results of treatment of primary atypical pneumonia with aureomycin or with the other broad-spectrum antibiotics have been interpreted uniformly as being favorable. The efficacy of these agents in this disease has therefore not gone unchallenged. Tillotson and Oseasohn,[56] in a critical summary of three series of aureomycin-treated cases, which they grouped as having been reported with controls, offered the following criticisms: the observations of Schoenbach et al.,[10] which appeared to show a significant reduction in the duration of fever in aureomycin-treated patients, were not considered valid because "the control and treated series are of questionable comparability in that the patients in each group were observed in different years"; they pointed

to the small series of "alternate treated and untreated patients" presented by Harvey and his associates,[48] in which no difference between the two was apparent, and they therefore implied that the results of this series were significant since this was the only alternated study cited in which a favorable result was not observed; the observation of Meiklejohn and Shragg[43] of some reduction in duration of the febrile period in their aureomycin-treated patients was also criticized because "the control series showed a much higher incidence of cold hemagglutinin titers than did the treated series" (to Tillotson and Oseasohn "this suggests the possibility that the untreated cases had a more severe disease than the treated cases for the following reasons: (a) the titer of cold hemagglutinins appears to be directly related to the severity of the disease, and (b) the data presented in other reports give no indication that aureomycin treatment suppresses the formation of antibody"); finally, they pointed to the failure of aureomycin to alter the course in a few patients as being highly significant in the absence of controlled studies. They therefore believed that the effectiveness of aureomycin in primary atypical pneumonia cannot be accepted without reservation.

Although these criticisms certainly have some validity, other features of these studies that are at least equally important in evaluating the data were not mentioned or were not given due consideration. Schoenbach and his co-workers[10] and others[7] have indicated the great difficulty in obtaining alternation or strict random selection of cases of primary atypical pneumonia, particularly in large general hospitals. The major thesis upon which the criticisms rest, however, is the wide variability and unpredictability of the course of primary atypical pneumonia.[57] From this point of view, the irregular and widely variable period of fever and symptoms in Schoenbach's "control" series following the administration of various therapeutic agents other than aureomycin when compared with the regularity with which these features of the disease improved, usually within two days of the beginning of treatment with aureomycin, takes on considerable and overriding significance. In these cases the total duration of illness was definitely and significantly less in the patients who were treated with aureomycin than in those not so treated. In this study the percentage of patients having significant cold hemagglutinin titers was somewhat higher (though not significantly) in the patients who did not receive aureomycin; however, the distribution of high and low titers, particularly in relation to the duration of the disease after the administration of aureomycin was started, is not given. The effect of aureomycin therapy on the development of cold agglutinins, therefore, cannot be adequately assessed from the data presented in this study.

The series of Harvey et al.[48] is so different from that of any of the others reported that it is difficult to evaluate. The reasons for this conclusion have already been mentioned in detail. The striking similarity (at the time of hospitalization or when the patients came under observation) between the aureomycin-treated and "control" cases in the series of Schoenbach and his associates[10] and between the penicillin-treated and aureomycin-treated cases in the series of Meiklejohn and Shragg[43] seem to be of considerable importance as evidence of random selection that was as good as feasible under the particular circumstances of these two studies. On the other hand, the evidence in the smaller series of Harvey et al.[48] suggests that the choice of cases was unduly weighted against the aureomycin-treated patients.

The interpretation of the higher incidence of significant titers of cold agglutinins in the penicillin-treated cases of Meiklejohn and Shragg as indicating a severer underlying disease in these cases seems to be unjustified on the basis of the data presented. The important manifestations of the disease in the penicillin and aureomycin groups were clearly comparable when treatment was started. To be sure, the frequency of occurrence of significant rises in cold agglutinins and the height to which these titers rise have been found to be correlated, in a general way, with the severity of symptoms, the extent of the pulmonary lesion and the duration and height of the fever.[47, 57] The lower incidence and lower titers observed in the aureomycin-treated patients may therefore be more reasonably interpreted as the result of the effect of aureomycin in limiting the severity of symptoms, the duration of fever and symptoms and the extent of the pulmonary lesion. These data may therefore be taken as important evidence favoring a specific action of aureomycin in limiting the infection; a similar inhibition of antibody formation has been demonstrated with antibiotic therapy in other infectious diseases in which they are highly effective, including Q fever.[46] The point made by Tillotson and Oseasohn[56] that no inhibition of antibody attributable to aureomycin has been recorded by others in primary atypical pneumonia is explainable by the simple fact that no direct and properly analyzed comparisons between parallel treated and untreated cases had been presented up to the time of their writing. The recent findings of Gallagher and Gallagher[55] give direct evidence that such a reduction in titers of cold hemagglutinins occurs in patients with primary atypical pneumonia who are treated with aureomycin. Whether this reduction is a direct result of inhibition of infection or is in whole or in part a reflection of other systemic or metabolic effects of aureomycin[58] cannot be determined from the data at hand.

One other point that has been brought up as strong evidence against accepting the available

data as indicating the effectiveness of aureomycin in primary atypical pneumonia is the fact that some cases have clearly failed to show any response. In a disease of known etiology or in one that is otherwise thoroughly and clearly defined, such evidence, particularly if it involved an appreciable proportion of cases, would be difficult to counter unless the failures could be adequately explained in each case, or at least in most of the cases. Because the failures have usually been reported in cases that were not clearly defined and have been very infrequent in cases that most clearly satisfy the rigid diagnostic criteria, this objection loses most of its weight. Unexplained failures from aureomycin therapy have also been noted in well authenticated cases of Q fever.[46] Such failures in primary atypical pneumonia emphasize the need for a clearer definition of the etiologic agent or agents of the disease and a more definite correlation of etiology with clinical and laboratory findings.

Tillotson and Ginsberg,[59] in pursuing the observation that most of the claims for the effectiveness of aureomycin in primary atypical pneumonia are based chiefly on the prompt response of the fever, have set out to determine whether this aspect might not be explained on the basis of an antipyretic effect of aureomycin. They interpreted their experiments in rabbits as demonstrating an antipyretic and hypothermic effect from the intraperitoneal injection of aureomycin in that animal. This effect they considered to be similar to that obtained with aminopyrine and therefore suggested that this was a possible explanation for the findings that have been interpreted as a favorable effect of aureomycin in atypical pneumonia. On the other hand, such an interpretation is inconsistent with the longer duration of the febrile period in the aureomycin-treated patients in the series from the Johns Hopkins Hospital,[48] which was taken to indicate that aureomycin is without effect in primary atypical pneumonia. Furthermore, an antipyretic action from aureomycin has not been observed in other febrile diseases, including many other established viral diseases, fungal infections, tuberculosis or infections with resistant bacteria, in which this antibiotic has no therapeutic effect.

Moreover, the response of the fever to aureomycin in patients with primary atypical pneumonia is decidedly different from that obtained with a known antipyretic such as aspirin. With this drug, experience has been uniformly unfavorable, at least in severe cases; the drop in temperature resulting from ingestion of a dose is, in my experience, quite regularly followed by a return of fever and symptoms in a few hours, with a repetition of the cycle after each administration of another dose of aspirin. In patients treated with aureomycin, on the other hand, there may be one or more swings in fever after treatment is begun, but these follow the pattern observed in the final days of the normal febrile course of the disease and do not occur in relation to the individual doses of the antibiotic. Finally, Harned et al.,[60] in their original pharmacologic studies, failed to demonstrate any antipyretic effect in controlled experiments in rabbits given aureomycin intravenously two hours after an intravenous injection of typhoid vaccine or in rats given aureomycin orally ten hours after subcutaneous injection of a dried-yeast suspension. Although Tillotson and Ginsberg[59] failed to demonstrate any significant peritoneal reaction from the topical injection of aureomycin, most observers have noted marked local tissue reactions from aureomycin in both man and animals that could conceivably account for the hypothermia that they observed.

Effect of Antibiotics on Eaton's Virus of Primary Atypical Pneumonia

This discussion would be incomplete if mention were not made of the studies of Eaton and his coworkers[61, 62] on the action of aureomycin, chloramphenicol and other chemotherapeutic agents on the virus of primary atypical pneumonia. In 1942 these workers isolated a virus transmissible to chick embryos, cotton rats and hamsters from the sputum and lungs of patients with this disease. Their filtration experiments indicated that this virus was of moderately large size and was distinct from the viruses of the psittacosis group and from Q fever. They presented evidence for the causal relation of the virus to primary atypical pneumonia by demonstrating an increase in neutralizing antibodies associated with the illness in approximately 60 per cent of over 100 cases tested. The specificity of the virus neutralization was supported by the failure to demonstrate the development of neutralizing antibodies for this virus in other acute respiratory diseases that could be identified by clinical or laboratory methods as influenza, psittacosis and bacterial pneumonias, and by the fact that the serums from the patients with atypical pneumonia did not develop demonstrable antibodies for other agents, including several respiratory viruses isolated from cotton rats and hamsters. Although there are no reports that these findings with Eaton's virus have been either confirmed or refuted by other workers, the chemotherapeutic studies made with the virus are of some interest.

Eaton's[61] experiments showed that aureomycin injected intraperitoneally starting twenty-four hours after intranasal infection of cotton rats with his virus of primary atypical pneumonia almost completely inhibited the development of pulmonary consolidation when given in daily doses of 1 mg. and was partly active at a dosage of 0.5 mg. per day. Therapeutic activity with doses of 2.0 to 5.0 mg. daily was also demonstrable when the beginning of treatment was delayed for five or six days. Chloramphenicol in doses of 5 to 20 mg. per day had only slight and irregular effects on the virus in

cotton rats under the same experimental conditions. Eaton also found that aureomycin inhibited the growth of his atypical pneumonia virus when injected into the yolk sac in two doses of 1 mg. each given two and forty-eight hours after amniotic inoculation of the virus. Eaton and his co-workers,[62] in additional experiments, showed that chloramphenicol inhibited the growth of his virus in chick embryos when injected into the yolk sac as a single dose of 5 mg. one hour after amniotic inoculation of the virus. If the virus with which Eaton was working is indeed one of the causative agents of primary atypical pneumonia, these controlled chemotherapeutic experiments in laboratory animals lend strong support to the evidence for the effectiveness of aureomycin in the clinical disease; they also suggest that, as in the case of infection with a psittacosis virus,[63] chloramphenicol is distinctly less effective, on a weight basis, than aureomycin.

Discussion

My own experience, like that of Schoenbach, Kneeland and many other authors working in large general hospitals, is limited to the observation of consecutive favorable responses in direct relation to aureomycin therapy. These experiences have, in turn, followed observations of similar cases studied during the preceding years either without antibiotics or chemotherapy or under treatment with penicillin or sulfonamides, or both. In these experiences it was uncommon to encounter patients in whom fever, acute symptoms and spread of pulmonary lesions continued for three days or longer after the institution of aureomycin therapy whereas longer duration of fever and symptoms occurred in the majority of patients after penicillin or sulfonamides or both were started or when the patients were observed and treated symptomatically and without antimicrobial agents. These observations, together with the results of such controlled studies as those of Meiklejohn and Shragg[43] and of the Gallaghers,[55] in patients who have characteristic clinical, laboratory and roentgenographic findings of a disease of at least moderate severity, and most of whom develop increases in titer of cold hemagglutinins offer strong and acceptable evidence of a favorable action of aureomycin in such cases of primary atypical pneumonia; admittedly this evidence is not absolutely conclusive and probably cannot be until the disease and its etiology are more clearly defined.

In the present state of understanding of this disease and in view of the difficulty of making fully controlled observations that would be completely convincing, in large general hospitals, such controlled studies may have to be carried out in schools, military installations or other types of institutions where patients can be seen early in the disease and observed and studied in great detail to establish the diagnosis by the most acceptable evidence. The opportunities for obtaining statistically valid data in these environments are much better because the types of patients are more uniform, epidemics are more apt to be encountered, the disease may be expected to show greater uniformity in its manifestation at any given time as compared with the kind of clinical material that is usually encountered in large community hospitals, the patients are less likely to receive other forms of therapy before they come under observation, specimens for serologic and other studies may more readily be obtained early in the disease and at suitable intervals thereafter, and absolute alternation or other types of random selection among patients treated with the agent under evaluation and those treated without specific therapy or with therapy known or supposed to be ineffective can more readily be achieved.

Conclusions

From this critical review of the available reports, it seems justifiable to consider that aureomycin is an effective agent in primary atypical pneumonia until more adequate and more thoroughly controlled data are obtained, perhaps in some such manner as has been indicated above, and such data show this assumption to be in error. Whether or not this antibiotic is used in any patient suspected of having this disease must be left to the clinical judgment of the physician. What has been said about aureomycin is probably equally true of terramycin. The evidence for the effectiveness of chloramphenicol is less extensive and somewhat less convincing, and that for streptomycin is much more controversial. Penicillin and sulfonamides are generally conceded to have no effect on primary atypical pneumonia.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38351

PRESENTATION OF CASE

A sixty-eight-year-old man was admitted to the hospital complaining of paralysis of the lower extremities.

At 3:00 a.m. on the day preceding admission the patient was awakened from sleep by a vise-like girdle pain about the lower chest and upper abdomen, associated with a feeling of numbness in the lower extremities. Considerable shortness of breath was noted, and he was unable to raise secretions properly. His physician administered 15 mg. of morphine three times over a period of two hours, after which the pain became dull, aching and less severe. Later in the morning paralysis and anesthesia of both lower extremities were noted. He did not void after the onset of the illness, and catheterization at noon of the day after onset of illness yielded 500 cc. of urine. Abdominal distention developed on the afternoon of the day after the development of symptoms, and an enema yielded only flatus. He was admitted to the hospital in the evening of the second day, some forty hours after onset of symptoms, for further study.

The patient denied the presence of hypertension or cardiac or pulmonary disease although some exertional dyspnea had been present for several years. He had had a "heavy cough" for the past two or three months productive of white phlegm but had otherwise been well.

Physical examination revealed an alert, well developed man lying propped up in bed in moderate distress from dyspnea, and repeatedly coughing with inadequate force to raise thick, mucoid sputum. The skin was cool and moist. Coarse rhonchi were heard through both lung fields, and medium coarse rales were present over the left side of the chest anterolaterally. No murmurs or thrills were present, and the pulse was regular. The abdomen was distended and tympanitic, but peristalsis was normal. Peripheral pulses were all palpable and equal. On neurologic examination the upper extremities were entirely normal. The patient was unable to move the lower trunk, pelvis or limbs, and could not contract the abdominal muscles. The lower extremities were flaccid. There was loss of pain and touch sensation below the level of the fifth dorsal segment bilaterally, with no sparing of sacral sensation. Vibration and position sense were completely absent from the iliac crests downward. Tendon reflexes of the lower limbs were weak bilaterally. Plantar response was flexor bilaterally. Abdominal reflexes were absent. The sphincters were not tested. No abnormal movements were noted.

The temperature was 101°F., the pulse 100, and the respirations 25. The blood pressure was 150 systolic, 98 diastolic.

The urine gave a ++ reaction for albumin; the sediment contained 3 white cells, 2 red cells and 2 granular casts per high-power field. The white-cell count was 12,000, with 80 per cent neutrophils, 14 per cent lymphocytes and 6 per cent monocytes, and the hemoglobin 12.5 gm. per 100 cc. The nonprotein nitrogen was 62 mg. per 100 cc. X-ray films of the chest taken in the supine and lateral position demonstrated clear lung fields. The heart shadow was enlarged in the region of the left ventricle. The aorta was tortuous and probably dilated. Anteroposterior films of the abdomen showed no abnormality. An electrocardiogram revealed a normal sinus rhythm of 75, with occasional auricular premature beats. It was considered an abnormal electrocardiogram with nonspecific changes in the ST segment and T waves, occasional premature auricular beats and intraventricular conduction time at the upper limits of normal.

An indwelling catheter was inserted, and the patient was started on digitoxin and given sedation. He continued to complain of aching pain over the lower chest, moderate dyspnea and great difficulty in raising thick secretions. This respiratory difficulty grew worse, and on the fifth hospital day it was noted that moving the patient slowed his pulse and turning him caused the pulse to disappear. Several hours later the patient died.

DIFFERENTIAL DIAGNOSIS

DR. H. THOMAS BALLANTINE, JR.*: I should like to review the history briefly and put it in better chronologic order. This sixty-eight-year-old man was considered to be well prior to the onset of the symptoms that brought him to the hospital. As a matter of fact, however, he had exertional dyspnea for many years and also a productive cough for a few months before entry to the hospital, neither of which apparently bothered him enough to cause him to consult a physician. However, at 3:00 a.m. on the day before admission, he was awakened from

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sleep by very severe pain — I say "very severe pain" because 15 mg. of morphine was administered three times by his physician before the pain became bearable. The chest pain was vise like and involved the lower thorax and upper abdomen. Coincident with or soon after the onset of pain, the patient noted numbness in the lower extremities and then rapidly developed paraplegia with a level on admission at the fifth dorsal dermatome. It is interesting that his usual exertional dyspnea became dyspnea at rest, the cough became much worse, and he was having a great deal of difficulty raising bronchial secretions.

At this point it might be interesting to speculate about the diagnostic possibilities. Degenerative disease as a cause of the paraplegia is so beyond the realm of possibility that I shall dismiss it immediately. I shall, however, concentrate on the causes of paraplegia because I think if I can explain that I can explain his hospital course and his death. Could the patient have had a tumor of the spinal axis? An extradural or an intradural tumor at about the level of the fifth dorsal dermatome could produce pain of the severity that was evidently present in this patient. However, it is highly unlikely that a tumor would not have given some prodromal symptoms of its presence even though the symptoms might not have been elicited until after the paraplegia occurred. The sudden onset of severe pain and the rapid onset of paraplegia make tumor unlikely.

Among infections I shall also discard without further comment meningitis because this is certainly not the history of a subarachnoid infection of the spinal cord. An extradural abscess could cause severe pain and rapidly appearing paraplegia; in fact it often does. Although I cannot discard the diagnosis of epidural abscess, I think both the severity of the pain and the rapidity of the onset of paraplegia were too great to make infection likely. On the same basis I shall discard a diagnosis of acute myelitis or intrinsic infectious disease of the spinal cord. Moreover, if the patient had myelitis, there should have been a pleocytosis in the spinal fluid, associated signs of meningitis such as stiff neck and some evidence of toxicity.

Vascular accidents — either primary or secondary — are the next consideration; by primary I mean hematomyelia, bleeding into the substance of the cord, which is a common complication of trauma and only rarely occurs spontaneously. The severity of the pain is against such a diagnosis, although it does not completely rule out hematomyelia. The rapidity of the development of symptoms certainly would make such a diagnosis tenable.

Thrombosis of the anterior spinal artery is another primary vascular accident that would fit any of the symptoms. The circulation of the spinal cord is such that the intercostal arteries, among others, supply one anterior spinal artery and two posterior spinal arteries, which in turn nourish the lower half of the cord. Thus, thrombosis of the anterior spinal artery could give a picture similar to this. Pain is often absent in this condition; at any rate, it is not a common finding. Furthermore, the anterior spinal artery supplies almost the entire substance of the cord with the exception, however, of the posterior columns, which are supplied by the posterior spinal arteries. If the anterior spinal artery were thrombosed, one would expect that position and vibration sense would have been preserved to a certain extent, whereas pain and temperature sense would have been absent and motor paralysis of the lower extremities manifest. From the protocol I get the impression that all sensory modalities were lost from the iliac crest downward, and it would be difficult to test position sense on the abdominal wall. This loss of all forms of sensation mediates against the diagnosis of thrombosis of the anterior spinal artery.

A third vascular process that might occur and affect the spinal cord secondarily is dissecting aneurysm of the aorta. A dissecting aneurysm that ruptured in the region of the thoracic aorta could strip off the intercostal arteries and thus interrupt the blood supply to the lower half of the spinal cord. Severe pain is characteristically seen with such a rupture, and the onset of symptoms is extremely rapid in this condition.

In turning to the physical examination and hospital course, I have two diagnostic categories in mind: infection and vascular accident. However, I have already almost ruled out an infectious process on the basis of the severity of the pain and the rapidity of onset of the paralysis. In addition, the temperature and white-cell count were such that infection is unlikely. The treatment the patient received in the hospital indicates that those taking care of him did not consider infection as a possibility.

Before and during his hospital stay the patient was dyspneic and produced white phlegm. I am impressed by the fact that the dyspnea and cough were considerably worse after the onset of the symptoms that brought him to the hospital; that would make me believe that there was some circulatory embarrassment added to the picture of the paralysis. The electrocardiogram changes although they were said to be nonspecific — certainly they are nonspecific to me — indicate some degree of cardiac damage; in a man of sixty-eight, I should suppose there was arteriosclerotic heart disease. The relatively low systolic blood pressure, 150, compared to the high diastolic pressure, 98, suggests that he had some degree of hypertension, but the blood pressure was probably not so high as it had been, owing to the shock of this cataclysmic process. He died from circulatory failure, with a nonprotein nitrogen of 62 mg. per 100 cc. — further evidence of cardiovascular renal disease. I do not think either hematomyelia or thrombosis of the anterior

spinal artery would increase a cardiac difficulty to this degree unless the level of the paralysis caused respiratory embarrassment. If that were the cause, however, it should have been possible to enhance the respiratory exchange by proper treatment. I shall have to say that hematomyelia and thrombosis of the anterior spinal artery are not the likely diagnoses.

May I see the x-ray films?

DR. JOHN L. SOSMAN: This is an anteroposterior film; you can see the findings mentioned in the protocol in spite of the difficulty in projection. The left ventricle is prominent; the aorta is quite tortuous and on the lateral film is rather far posteriorly and is then lost. The fact that I do not see clearly, at any point, the descending portion of the aorta is suggestive but not indicative of dissecting aneurysm. Also, I think it is definitely widened here. There is no definite calcification in the aorta in this film. The film of the abdomen shows nothing but ileus of a moderate degree.

DR. BALLANTINE: Even when peristalsis is present, ileus is often seen after the rapid onset of paraplegia.

I am considerably relieved; the x-ray report in the protocol had worried me. Weisman and Adams,* who reviewed the experiences at the Boston City Hospital in cases of dissecting aortic aneurysm, made the point that the aorta is widened and laid great stress upon that as a sign of dissecting aortic aneurysm. I investigated this problem a little further and found that according to our radiologists, dissecting aneurysm of the aorta is sometimes seen with little or no demonstrable widening. There is one other thing I must comment upon: the peripheral pulses were said to have been present, and the extremities were of good color. That is an unusual finding in dissecting aneurysm of the aorta because usually there is some blockage to the flow of blood to the lower extremities; often, indeed, the dissection will go to one or both of the iliac arteries. However, it is possible to have a medial dissection by a sudden rupture of the intima, which will encircle the aorta and leave a central channel through which blood may pass to the lower extremities; I shall have to assume that such a dissection occurred in this patient.

In summary, this elderly man had, I think, good evidence of fairly extensive cardiovascular renal disease, which set the stage for the development of dissecting aneurysm. He died in cardiac failure as the result of the pre-existing cardiac damage, the effect of dissecting aneurysm on the circulation and the effect on respiratory exchange of paralysis of the abdominal muscles and the lower intercostal muscles.

DR. SOSMAN: Would you comment on the terminal event, when turning him caused the pulses to disappear. Is not that consistent with a further development of the same thing?

DR. BALLANTINE: I omitted that because I was not able to explain it properly. The explanations that occur to me are that the dissection went up the carotid artery or that in some other manner the carotid sinus was stimulated, which would cause the pulses to slow and eventually to disappear. What other effect turning him in bed would have on the circulation, I think you ought to ask the cardiologists.

DR. WILLIAM N. TIMBERLAKE: I believed, too that the sudden onset of severe pain and paralysis indicated a dissecting aneurysm, and the patient was admitted to the hospital for confirmation of that diagnosis.

CLINICAL DIAGNOSES

Dissecting aneurysm of aorta.
Infarction of spinal cord.

DR. BALLANTINE'S DIAGNOSES

Dissecting aneurysm of thoracic aorta.
Infarction of spinal cord.

ANATOMICAL DIAGNOSES

Dissecting aneurysm of thoracic and abdominal aorta.
Infarction of spinal cord.
Cardiac hypertrophy, hypertensive type.
Pulmonary edema.

PATHOLOGICAL DISCUSSION

DR. ROBERT H. FENNELL, JR.: We did find at autopsy that there was a dissecting aneurysm of the descending aorta — primarily in the thoracic but extending into the abdominal portion. The intimal tear was in the descending thoracic aorta several centimeters below the level of the origin of the left subclavian artery on the anterior wall. The dissection extended posteriorly to occlude the intercostal arteries and downward to involve the upper lumbar arteries. There was quite a large hematoma in the periaortic tissue, but it was confined to a relatively small area and was posterior and lateral. The dissection did not involve the celiac axis and the superior mesenteric artery, since it was posterior at this level and stopped just below the renal artery. Proximally, the dissection extended to the level of the left subclavian artery. The heart was large; it weighed 580 gm. — a characteristic hypertensive heart. Microscopically, we noted in the aorta the cystic medionecrosis, which often forms a background for the dissection. There was moderate pulmonary edema.

Dr. Rosales will tell you about the findings in the central nervous system.

*Weisman, A. D., and Adams, R. D. Neurological complications of dissecting aneurysm. *Brain* 67:69-92, 1944.

DR. REMEDIOS ROSALES: The brain, both externally and on section revealed no abnormality except for severe atherosclerosis of the cerebral arteries. The spinal cord was softened from about the level of the fourth to the tenth or eleventh dorsal segments. Sections of the cord in this region showed that there was not the usual demarcation between the gray and white matter; sections above and below appeared normal. Microscopical examination of the softened portion of the cord showed lesions varying in extent and severity from one segment to the next. At all levels of the diseased cord the lesions involved the posterior horns and lateral columns. In some segments, there was in addition involvement of the posterior columns, the remainder of the gray matter and the medial portions of the anterior white columns. In these lesions, there was complete destruction of the parenchyma and supporting elements, along with degeneration of the myelin. The few remaining neurons were swollen and pale staining with dark, pyknotic nuclei. There were a few polymorphonuclear leukocytes and some macrophages in the destroyed parts of the cord.

A PHYSICIAN: Was a lumbar puncture done?

DR. TIMBERLAKE: No.

DR. RAYMOND D. ADAMS: Dr. Ballantine's analysis of the neurologic findings impresses me as being entirely correct. Surely, we are dealing with an acute lesion of the spinal cord producing a paraplegia and paralytic ileus. The change in systemic circulation may have been related to the extensive disease of thoracic segments affecting the autonomic nervous system — that is, the preganglionic neurons. The loss of tendon reflexes in the legs and the flaccidity were probably due to "spinal shock." The fact that the plantar reflexes were flexor should also be commented upon. Sometimes after spinal shock due to a lesion of the cervical or thoracic segment of the spinal cord, the first muscles to regain any reflex function are those most removed from the lesion — that is, those controlled by the lowest sacral segments. The flexor muscles of the feet are innervated by a lower segment than the extensor ones, and in them, flexor response therefore precedes extensor.

The neurologic disturbances resulting from dissecting aneurysm are helpful in diagnosis. From observation of a number of these patients three syndromes have emerged: the first, which Dr. Ballantine has so clearly explained, is ischemic myelopathy due to interruption of the intercostal arteries; the second is the occlusion of one or both carotid arteries by the dissecting aneurysm, causing sudden hemiplegia, aphasia or coma; and the third, the most common syndrome, is the blockage of the circulation to a limb, either arm or leg or both legs, with ischemia of the peripheral nerves. In the last condition the affected limb is pulseless. The occurrence of these neurologic syndromes in conjunction with severe thoracic or abdominal pain should always suggest the diagnosis of dissecting aortic aneurysm.

CASE 38352

PRESENTATION OF CASE

A seventy-five-year-old man entered the hospital because of vomiting of coffee-grounds material.

The patient had been known to have diabetes for about fifteen years, had been taking protamine zinc insulin, 20 to 30 units daily, and had been following a diabetic diet as well as he could. About two years prior to entry a cataract of the left eye was extracted. At that time he gave a history of dyspnea on exertion and ankle edema; examination revealed clear lungs, a normal heart, a blood pressure of 190 systolic, 95 diastolic, and a +++ reaction for albumin in the urine. He was next seen one and a half months before admission in the Out Patient Department because of ulceration of the heels present for two weeks. He had not tested his urine for sugar for a number of months but had continued to take 30 units of protamine zinc insulin daily. The exertional dyspnea had been worse and he had experienced sharp shooting pains in both legs for the preceding two or three months. Examination at that time revealed severe diabetic retinitis, clear lungs and slight cardiomegaly, with a Grade II apical systolic murmur, a liver palpable 3 fingerbreadths below the costal margin and +++ ankle edema. He refused hospitalization, but was admitted to a nursing home, where he stayed for four and a half weeks and allegedly did fairly well. During the last ten days in the nursing home, he had had some epigastric pain, with radiation substernally upward to the throat. About ten days prior to entry, he left the nursing home; since then, he had had episodes of vomiting every night. Four days before admission he began to vomit everything he ate, as well as coffee-grounds material. He also passed a number of grossly bloody stools during the three days prior to entry. He became progressively weaker and developed dyspnea, orthopnea and an increase in ankle edema. There was no history of previous gastrointestinal complaints.

Physical examination revealed a thin, moderately pale man with moderate dyspnea and orthopnea. The skin was cool and sweaty. The neck veins were distended. Moist rales and rhonchi were heard throughout the left side of the chest and there were signs of fluid at the right base. The heart was somewhat enlarged, with distant heart sounds. The abdomen was flat, soft and relaxed, and peristalsis was slightly decreased. A tender liver edge was palpated 4 fingerbreadths below the

costal margin. There was ++++ ankle edema. Pulsations were absent below the level of the femoral arteries.

The temperature was 100, the pulse 88, and the respirations 32. The blood pressure was 100 systolic, 50 diastolic.

The urine gave a green sugar reaction and a +++ reaction for albumin; the sediment contained 5 to 10 white cells per high-power field and many hyaline and granular casts. Examination of the blood showed a hemoglobin of 9 gm. per 100 cc. and a white-cell count of 16,800, with 92 per cent neutrophils; the platelets were normal.

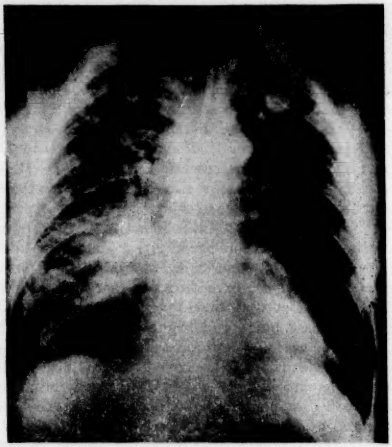

FIGURE 1.

The blood pH was 7.4. The fasting blood sugar was 192 mg., the nonprotein nitrogen 56 mg., the total protein 6.02 gm., and the total cholesterol 278 mg. per 100 cc.; the carbon dioxide was 25.4 milliequiv., the sodium 136.9 milliequiv., the potassium 5.8 milliequiv. and the chloride 96 milliequiv. per liter. The vomitus and stools gave ++++ guaiac reactions. An electrocardiogram showed normal sinus rhythm at a rate of 70, a PR interval of 0.14 second, and a QRS interval of 0.08 second; the ST segments were sagging and the T waves flat in Leads 1, 2, 3, AVL, AVF, V_4, V_5 and V_6; the ST segments were slightly elevated, and the T waves low and inverted in Leads AVR and V_1; the ST segments were slightly elevated, and the T waves upright in Leads V_2 and V_3.

Roentgenograms of the chest demonstrated moderately engorged pulmonary vessels, a small amount of fluid in the right costophrenic angle, a tortuous calcified aorta and prominence of the left ventricle of the heart; the right lung appeared relatively dense, and there were some increased linear densities in the left-lower-lung field (Fig. 1). An x-ray film of the abdomen showed normal renal outlines, bowel pattern and bone density.

The patient was treated with digitalis, oxygen and Mercuhydrin. All urinary sugar reactions were blue or green. The vomiting stopped, and the hematocrit readings remained around 30 per cent throughout his stay. However, he continued to be critically ill and became more dyspneic and cyanotic, choking and gasping when out of the oxygen tent for even a minute. On the third day he complained of an empty feeling in the stomach and pain in the calves; there was no redness, tenderness or swelling. The nonprotein nitrogen was 80 mg. per 100 cc. On the third day the temperature was 101°F., and the breath sounds were diminished throughout the left lung; penicillin and later streptomycin were added to the treatment. An electrocardiogram showed changes consistent with digitalis effect. He continued to have a few tarry stools, and incomplete aeration of the lower-lung fields and finally died on the seventh hospital day; on the day prior to death the nonprotein nitrogen was 160 mg. per 100 cc.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES H. DUTOIT*: In summary this was an elderly man, with long-standing diabetes and certain degenerative complications such as diabetic retinitis. In the few months before admission evidence of arterial insufficiency in the legs had developed. He had had a two-year history of symptoms pointing to cardiovascular renal disease. He is known to have had slight hypertension. When first seen he had shortness of breath and ankle edema, but he did not have unequivocal evidence of congestive heart failure on physical examination. The edema and the albuminuria could have been due to Kimmelstiel–Wilson disease (intercapillary glomerulosclerosis), but could just as well represent hypertension with a certain amount of myocardial insufficiency or nephrosclerosis or chronic pyelonephritis. Four and a half months before admission he had symptoms of arterial insufficiency in the legs. He also had an increase in the respiratory difficulty, a large liver, more ankle edema and a change in the size of the heart, as well as a murmur, which apparently had not been present two years previously. All these findings probably indicate a certain degree of congestive failure. Ten days prior to admission, symptoms referable to a new system appeared — that is, pain radiating upward to the throat from the epigastrium and vomiting of both food and coffee-grounds material, as well as bloody stools.

*Clinical and research fellow in medicine, Massachusetts General Hospital.

On physical examination he had distended neck veins, signs of fluid at the right base, rales in the left side of the chest, an enlarged heart, distant heart sounds, an enlarged tender liver and massive ankle edema; all these signs suggest congestive heart failure. Nothing found on physical examination gave any clue to the cause of the hematemesis and melena. No masses were palpated in the abdomen other than the liver. The spleen was not enlarged. There was no suggestion of intestinal obstruction or peritoneal irritation. The laboratory data are only in keeping with what one would expect in an elderly diabetic patient with some pre-existing renal disease and a fulminating illness. The blood chemical data indicate that uremia probably played no great part in the picture. The electrocardiogram was not diagnostic.

May I see the x-ray films?

DR. J. LAURENCE SOSMAN: The single examination of the chest and abdomen was made with the patient, who was quite sick, lying down; consequently, its usefulness is limited. The pulmonary vessels are engorged on the right; there is definite fluid at the right base and possibly pulmonary edema. This film, partly because of the position of the patient and partly owing to spread of fluid throughout the thoracic cavity, cannot be evaluated. The increased density may be due entirely to the fluid in the right base, spreading over the lung and obscuring it. In view of the amount of pulmonary congestion seen on the left, the appearance of the left lung is a little unusual — it is quite clear. The vascular markings are diminished. That the hilus is not at all prominent suggests that something may be occluding the pulmonary arteries on the left (Fig. 1). The question was raised whether that could be due to a retrograde spread of tumor; however, no one whom I asked in the Department of Radiology could recall a case as extensive as this that was also unilateral.

The abdomen, except for the low position of the liver, shows nothing suggestive of specific disease. There is some calcification of the abdominal aorta. There is some irregularity in the medial half of the stomach but not enough to be diagnostic. This man was not well enough to undergo the usual examinations of the gastrointestinal tract.

DR. DUTOIT: It is somewhat difficult to relate the entire picture to diabetes with degenerative complications such as are seen particularly in the older age group. Diabetic persons sometimes develop a dilated stomach that can lead to the vomiting of a certain amount of coffee-grounds material that is guaiac positive. This, I believe, is as a result of a secondary gastritis. Yet the degree of the melena and hematemesis in the case under discussion are out of keeping with such an interpretation.

The diagnosis that comes to mind in connection with the underlying vascular disease is a vascular accident occurring in the abdomen. It is hard to imagine that a mesenteric occlusion sufficiently large to produce bleeding for seventeen days would not have produced signs of intestinal obstruction. It is equally hard to assume that an occlusion of a mesenteric vessel with infarction of the bowel sufficiently large to release this much hemoglobin into its lumen could occur without causing a much more profound disturbance in electrolyte balance than this patient had. I suppose that such a lesion could occur in the duodenum without presenting obvious signs of small-bowel obstruction. The picture in the chest — increasing respiratory symptoms with definite signs of congestive failure — makes one think of heart disease with endocardial involvement and subsequent emboli to the bowel. Again, such events usually produce quite a different clinical picture than this. I am left with the conclusion that the gastrointestinal symptomatology is not related to the vascular disease. The statistically most common explanation is a peptic ulcer. It is true that the patient's blood loss persisted over a longer period than is usually seen in bleeding from an ulcer. One could postulate a certain amount of bleeding from the ulcer, together with pyloric obstruction and secondary gastritis. A malignant process is quite definitely possible.

I think that the trouble was either low in the stomach near the pylorus or below it since the vomiting of food occurred before the vomiting of coffee-grounds material. The blood in the stool was also more prominent than that in the vomitus. There is no evidence to locate the lesion in the small or large bowel. A malignant lesion of the stomach is a distinct possibility.

A carcinoma of the pancreas sometimes produces this type of picture by eroding into the stomach or duodenum. In a patient like this, even if the signs of congestive failure are quite definite, rapidly progressive dyspnea especially when combined with cyanosis indicates a possible noncardiac complication. One is tempted to speculate about the possibility of lymphatic spread of tumor through the lungs; the commonest source of such a complication is the pancreas. Although the history is usually longer, such patients have quite explosive respiratory failure followed by right-sided heart failure, which becomes extremely difficult to distinguish from the more usual picture of left-sided congestive heart failure. The right-sided failure may occur as a result of thrombosis of the small vessels superimposed on the process spreading through the lungs. The history is usually longer, and the x-ray findings are usually quite distinctive in cases of that sort. I looked carefully for evidence to back up such a diagnosis and did not find any.

Other causes of gastrointestinal bleeding are hiatus hernia and portal hypertension, with varices in the esophagus or even in the stomach. Neither of these seems very likely.

To return to the thorax, there was definite evidence of congestive heart failure. The patient had distended neck veins and undoubtedly a change in the size and sounds of the heart. A renal element may also have played a part in the edema, but I wonder, in view of the rapid development of respiratory failure, if there had been some additional process such as one or more episodes of massive pulmonary embolization. There is just a hint in the x-ray film of such a process. This, of course, would not readily explain the melena. However, bleeding itself predisposes to venous thrombosis, as does peripheral vascular disease, both of which this patient had. Carcinoma of the pancreas also predisposes to thrombotic episodes.

My diagnosis is massive pulmonary infarcts superimposed on a certain amount of coronary-artery disease in an elderly diabetic patient with diabetic and hypertensive changes in the kidneys. Cancer of the stomach is my first choice, as a cause of the melena, cancer of the pancreas my second, and peptic ulcer my third. As a long shot, a bizarre vascular accident such as the rupture of an aneurysm into the mesentery of the bowel should be included.

A PHYSICIAN: Isn't that rather long for the patient to be on the right side? Could that x-ray picture have been due to edema of the lung from the patient's lying so long on the right side?

DR. SOSMAN: There may be an element of edema, but he also had pleural fluid, and some of it may have been due to the spread of the fluid in the pleural space. It should be remembered that the film was taken with the patient lying on his back.

CLINICAL DIAGNOSES

Diabetes mellitus.
Diabetic nephropathy.
Arteriosclerotic heart disease, with congestive heart failure.
Gastrointestinal hemorrhage from peptic ulcer.
?Pulmonary embolism.
Bronchopneumonia.

DR. DUTOIT'S DIAGNOSES

Massive pulmonary embolism.
Coronary-artery disease, with congestive heart failure.
Diabetic or hypertensive nephropathy or both.
Cancer of stomach.
?Cancer of pancreas.
?Peptic ulcer.

ANATOMICAL DIAGNOSES

Perforated gastric ulcer.
Coronary-artery disease, with early myocardial infarction.
Peritonitis, acute.
(Diabetes mellitus.)
Nephrosclerosis.
Intercapillary glomerulosclerosis.
Cardiac hypertrophy.
Hydrothorax, bilateral.
Fatty changes in myocardium.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The heart in this case was quite interesting on gross examination. A yellowish mottling was present throughout the entire myocardium of the left chamber. At first we thought this mottling was diffuse infarction of the entire myocardium, but at a closer inspection it reminded us of the tigering seen in the fatty changes in the hearts of patients with anemia. This patient was not very anemic except toward the end; I have never seen that much fatty change with acute anemia. The other suggestion about the cause of the tigering was that it may have been the fatty change described by Mallory et al.* in wounded soldiers. They reported that the fatty deposits are never seen on gross examination but only microscopically in the heart, the liver and the kidneys usually between the third and the seventh or eighth day of shock; in those cases the patients had died of injuries during the war. I do not know that we can explain the changes in the case under discussion. Some of the sections of the myocardium showed acute myocardial infarction in addition to the fatty change. The coronary arteries were extremely sclerotic and narrowed, but no fresh occlusion was observed. The heart weighed 430 gm. and was consistent with a mild degree of hypertension.

The lungs were edematous and contained no pulmonary emboli. There was pleural fluid on both sides. The kidneys showed a severe degree of nephrosclerosis and the intercapillary glomerulosclerosis, which was quite widespread; I should guess that most of the renal failure was due to the nephrosclerosis rather than to the intercapillary glomerulosclerosis.

The immediate cause of death was a perforation of a gastric ulcer. There were three acute peptic ulcers; one, measuring 4 cm., located about 3 or 4 cm. from the pylorus, had perforated, probably while the patient was in the hospital, producing a localized peritonitis, with some spread to the general abdominal cavity.

A STUDENT: How frequently is tarry stool seen with ulcers that perforate?

DR. CASTLEMAN: That is not very common. Most of the patients with tarry stools have ulcers in the posterior duodenal wall; those are the ones that do not perforate. Those that rupture are in the anterior wall, as this was, along the lesser curvature.

A PHYSICIAN: I should like to ask if this fatty infiltration might be a complication in a diabetic patient.

DR. CASTLEMAN: We have not seen it before.

*Mallory, T. B., et al. General pathology of traumatic shock. *Surgery* 27:629-644, 1950.

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PRIMARY ATYPICAL PNEUMONIA AND COLD AGGLUTININS

In the fully developed disease and in a thoroughly studied case the diagnosis of primary atypical pneumonia, or viral pneumonia, as it is now understood, can readily be made — and with considerable assurance. In the milder forms, or in the early stages of this disease, however, this diagnosis may be difficult and often impossible to make with any degree of confidence. Moreover, although the etiology is almost certainly a filtrable virus,[1] such a virus cannot be isolated from the patient, and it is not available for use in serologic tests to determine the development of specific antibodies; a specific etiologic diagnosis, therefore, cannot be made even retrospectively.

As a result, and for practical purposes, a reliable diagnosis of primary atypical pneumonia is usually made on the basis of certain data, some of which are negative and some positive. On the negative side it is necessary to exclude the following: a possible bacteriologic etiology by study of the sputum and blood for respiratory pathogens; known viral or rickettsial agents that may cause respiratory infections — particularly the agents of influenza, psittacosis and Q fever — by attempts to isolate these agents, or more practically by serologic tests of blood specimens taken in the acute and convalescent phases for the development of specific antibodies against these agents; and other causes, such as fungal, parasitic, allergic and rheumatic, as far as possible through appropriate studies.

On the positive side it is necessary, first of all, to have the characteristic symptomatology and physical, roentgenographic and clinical laboratory findings. These, unfortunately, are not specific, and it is because they so closely resemble those found in cases of known etiology, particularly the nonbacterial causes, that it is necessary to exclude the other possible etiologies; practically, however, this is not usually done except when some specific agent or cause is suspected. Of the diagnostic laboratory tests only the demonstration of a significant rise in the titer of cold hemagglutinins or of Streptococcus MG agglutinins has proved very helpful, but neither of these is highly specific. Although there is by no means universal agreement on this matter — nor can that be expected in the nature of things — the cold-agglutinin test has generally proved to be the simplest and most reliable one for the diagnosis of cases of moderate or more than moderate severity; this has been particularly true in areas where the disease has been unusually prevalent. Strong evidence in favor both of the filtrable nature of the etiologic agent in some cases of primary atypical pneumonia and of the close association of the development of cold hemagglutinins with the etiologic agent in those cases comes from the studies on the experimental transmission of this disease. Patients who have been experimentally infected with a filtrate of infectious material from a donor patient who had the characteristic clinical disease with the development of

cold agglutinins not only showed the same clinical picture but also manifested significant rises in titer of cold hemagglutinins.[1]

The evaluation of antimicrobial therapy in primary atypical pneumonia has been hampered by the practical difficulties in establishing a diagnosis, particularly early in the disease; the wide variations in the natural course unaffected by therapy, especially at different times and in various situations; and, perhaps as a consequence of these facts, the variable results reported with respect to the development of cold agglutinins. Consequently, although workers who have had the most intensive experience with severe cases, such as those likely to be encountered in large civilian hospitals, have come to the conclusion that the broad-spectrum antibiotics, particularly aureomycin, are highly effective and beneficial in atypical pneumonia, opinion among other workers has been divided. The controversy has recently been extended to include the question of the efficacy of streptomycin, although there seems to be universal agreement that the sulfonamides and penicillin are not effective.

A critical review of the literature dealing with this aspect is presented in the report on Medical Progress in this issue of the *Journal*. The controversy stems, in part, from the fact that most of the early favorable reports on the beneficial effects of aureomycin were based on observations made in successive series of cases observed by the same person under similar circumstances but at different times and were not accompanied by simultaneous observations in parallel and contemporary controls. However, it is pointed out that even the reports that were considered by their authors to have been carefully controlled have not all been significant or reliable. Proper random selection for comparisons of treated and control groups is most difficult in the early stage of this disease, and that is the time when treatment with the test and control agents should be started to demonstrate the greatest and most significant differences. In the early stages of primary atypical pneumonia, the findings frequently resemble those of undifferentiated acute respiratory disease, which more often may be expected to be mild and have a brief course even without antimicrobial therapy.

The development of cold agglutinins among treated and control cases should also prove useful in the evaluation of the effectiveness of therapy. The results of this test could, first of all, help in establishing the diagnosis in both treated and control groups and thus offer an important indication of whether the cases in each group are comparable, at least in this diagnostic feature. The possibility exists, however, that the development of cold agglutinins will be delayed or inhibited by antimicrobial therapy effective against the etiologic agent. Such a possibility was suggested in the controlled study on aureomycin by Meiklejohn and Shragg[2] and has been clearly brought out by Gallagher and Gallagher in their study reported elsewhere in this issue.

Although the number of cases reported by the Gallaghers was small, their observations were carefully made and controlled, and their results are clear and significant. Cold agglutinins in significant titers developed in all the patients. In the patients who were not treated with aureomycin, cold agglutinins were demonstrated earlier in the disease, the maximum titers that they attained were higher, and significant titers persisted for a longer time when compared with the findings in the alternate patients who were treated with aureomycin. Incidentally, their findings also confirmed the beneficial effects of aureomycin on the clinical course of the disease.

If the cold agglutinins are in any way related to the development of antibodies against the etiologic agent of primary atypical pneumonia — a large assumption, to be sure, and yet not an unreasonable one — inhibition of multiplication of that agent and hence removal of some of the antigenic stimulus may be expected to reduce the total antibody response. The fact that levels of the cold-agglutinin titers are directly influenced by the height and duration of fever and by the severity of the disease lends support to this assumption. Since it is difficult early in the course of atypical pneumonia to predict the duration and severity and since the aureomycin treatment in the cases reported both by Meiklejohn and Shragg and by the Gallaghers was started early in the disease, the findings of these observers may be interpreted as consistent

with a specific inhibiting effect of aureomycin on the etiologic agent of primary atypical pneumonia. The final proof of the validity of this interpretation must await more definitive knowledge concerning the etiologic agent.

References

1. Commission on Acute Respiratory Diseases. Transmission of primary atypical pneumonia to human volunteers. *J. A. M. A.* **127**:146-149, 1945.
2. Meiklejohn, G., and Shragg, R. I. Aureomycin in primary atypical pneumonia: a controlled evaluation. *J. A. M. A.* **140**:391-396, 1949.

PLASMA SUBSTITUTES AND DEFENSE

The FCDA (Federal Civil Defense Agency) has recently placed a large order for periston to be stockpiled for use after a major disaster. This step not only indicates definite progress in medical preparedness but also marks the transition of plasma substitutes from the investigative phase in the laboratory to the sphere of clinical usefulness.

It is easy to criticize the Federal authorities for being slow in providing a plasma substitute. Since the outbreak of hostilities in Korea the country has lain under the shadow of impending atomic attack. Plasma has not been available in sufficient quantities to treat the victims of widespread bombing, nor is it likely to be. Yet the FCDA and the National Research Council balanced the imminence of the danger against the necessity for thorough investigation of various plasma-volume expanders and chose to investigate before stockpiling. The wisdom of this decision is now apparent. In World War II plasma was distributed to the armed forces under the misconception that it would adequately replace whole blood and was completely harmless. These assumptions were costly in lives. It took a considerable time before plasma assumed its proper place as a therapeutic agent.

Over two years of investigation in a variety of laboratories and hospitals by means of chemical analysis, animal experimentation and carefully controlled clinical usage have fairly well established the properties of the various plasma substitutes. Their efficacy and limitations in treating both hemorrhagic and nonhemorrhagic shock are now understood, and their stability and their untoward effects have been documented. The investigative phase is by no means at an end. Further changes in the molecular size of these agents are being investigated; other materials such as various polysaccharides and protein compounds are being subjected to experimentation. It is possible to visualize other substances or periston in a different form, ultimately better than what is now being made, but this material is the first to fill the minimum requirements of an adequate blood-volume expander so that no matter what is produced later, it will retain its usefulness.

A plasma substitute in its ideal form approximates plasma in its ability to restore and maintain the cardiac output, arterial pressure and blood volume of a patient in shock. It must be nonpyrogenic, noninfectious, nonantigenic and nontoxic, must cause no allergic reactions, must not be stored in the body and must cause no harm to the body tissues. If it can be partially or wholly metabolized it is more useful, but for the treatment of shock this is not an essential characteristic. From the point of view of civil defense such a material must be stable under all conditions, easily transported, stored and administered, available in abundant quantities and above all cheap to manufacture.

Considered in the light of these criteria, why was periston chosen? Although any liquid tolerated by the body when given intravenously could be called a plasma substitute, only those approximating plasma in their abilities to exert and maintain colloidal osmotic pressure are of any real value. This narrows the field to globin, gelatin (both osseus and pig-hide), dextran (also called Macrodex or Intradex), pectin, albumin (diluted) and periston (also called PVP-Macrose, kollidon, subtosan or polyvinylpyrrolidone).

Globin, retrieved from red cells after the removal of plasma, is attractive to the thrifty because it represents the salvaging of a waste product. It is more expensive to produce than some of the other substitutes and less effective in restoring blood pressure.

Gelatin gives great promise. It is more expensive than periston, but is less apt to be stored in the body or cause cell damage if used in large quantities. In its present form it gels below room temperature, but this defect can be corrected. It has

been less widely used than periston but might ultimately supplant it.

Dextran, in the imported form, has been pyrogenic. It is potentially antigenic. As produced domestically, by bacterial degradation of beet sugar, it is not pyrogenic, but more expensive to produce and the supply as yet is inadequate.

Pectin is still being investigated.

Albumin is only available in small quantities and is expensive to produce.

Periston, a derivative of acetylene, was used over 500,000 times by the Germans in World War II. It was highly pyrogenic, the mean molecular weight was too great, and the range of molecular size was too wide. A large stockpile of the powdered material is on hand in this country. As it is now produced its mean molecular weight is smaller, and it is more homogeneous. It is not pyrogenic. It is stored in the tissues, with possible cell damage if large amounts are used. Its particular advantages are its stability, ease of administration and extreme cheapness to produce — it costs less than $2.00 for 500 cc. If the pharmaceutical company charged with the production of 1,200,000 units for the FCDA can produce it rapidly, the problem of the availability of a plasma substitute will be solved. After this, the Food and Drug Administration will have to pass on it before the states are allowed to purchase it. The Blood Section of the Massachusetts Civil Defense Agency has advocated its purchase for use in aid stations for some time. It does not require reconstitution as dried plasma does, and it is unaffected by low temperature. If available in large quantities, it can effectively combat shock to permit transportation of the injured to hospitals where whole blood would be available. Its advantages dwarf into insignificance its side effects. It is hoped that it will soon be available.

UNIVERSITÉ LAVAL

THE year before Harvard University was founded in 1636 as an academy for godly young men in Cambridge, Massachusetts, the Jesuit fathers had already established a college in the French city of Quebec. Twenty-eight years later this institution of learning became Quebec Seminary, under the guidance of the pioneer bishop François de Montmorency Laval.

This was the first organized effort at higher education to be made in Canada, and for many years it flourished only as a college for theology and the arts. Medicine in Canada, as indeed in most places in the world, continued to be taught by precept and example, through the medium of apprenticeship. Even under British rule this pastoral relation continued in an agricultural country, although university diplomates in medicine began to arrive from England, Scotland and Ireland, and more young men turned for their medical education to the old schools of London and Edinburgh, and the new ones of Philadelphia, New York and Boston.

Finally, in 1823, the first organized Canadian medical school was established as the Montreal Medical Institute, to become McGill University Faculty of Medicine in 1829; in 1843 the University of Montreal Faculty of Medicine was created, and in the same year the Medical Faculty of King's College came into being, later to become the University of Toronto Faculty of Medicine.

Following shortly on the establishment of these schools the Quebec School of Medicine was organized in 1848, becoming the Faculty of Medicine of Laval University when Quebec Seminary received its Royal Charter in 1852 and achieved university status.

This fall the eyes of the academic world will turn toward the Cité Universitaire above the St. Lawrence, when the centenary celebrations of Laval University and its medical school will reach their peak. Then, from September 19 to 22, an international convocation will bring together at Quebec delegates from universities throughout the world, from the Vatican and from the governments of France and Great Britain, unmindful of their countries' historic conflict on the plains of Abraham.

Messrs. James Miller & Co., Bromfield Street, in this city, have lately imported the celebrated laced stockings, so highly recommended in cases of varicose veins.

Boston M. & S. J., *September 1, 1852*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

DAVIS — Lincoln Davis, M.D., of Needham, died on July 29. He was in his eighty-first year.

Dr. Davis received his degree from Harvard Medical School in 1898. He was formerly chief of the East Surgical Service at the Massachusetts General Hospital, president of the Harvard Medical Alumni Association, vice-president of the American Surgical Association and president of the Greater Boston Medical Society. He was a fellow of the American College of Surgeons and American Medical Association and a member of the New England Surgical Society, and was a former president of the Boston Medical Library.

He is survived by his widow, two sons and two daughters.

MCALLESTER — Ralph W. McAllester, M.D., of Everett, died on July 31. He was in his seventy-fifth year.

Dr. McAllester received his degree from Harvard Medical School in 1904.

He is survived by a daughter and three sons.

PARK — Francis E. Park, M.D., of Newton Center, died on August 5. He was in his eighty-sixth year.

Dr. Park received his degree from Harvard Medical School in 1894. He was a fellow of the American Medical Association.

He is survived by his widow, a son, two daughters, five grandchildren and a sister.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The September Schedule of the Consultation Clinics for Crippled Children in Massachusetts is as follows:

ORTHOPEDIC CLINICS	DATE	CLINIC CONSULTANT
Gardner	September 2	Carter R. Rowe, M.D.
Haverhill	September 3	William T. Green, M.D.
Greenfield	September 4	Charles L. Sturdevant, M.D.
Lowell	September 5	Albert H. Brewster, M.D.
Salem	September 8	Paul W. Hugenberger, M.D.
Lynn*	September 8	Daniel M. Killoran, M.D.; John J. Crowley, M.D.
Brockton	September 11	George W. Van Gorder, M.D.
Springfield	September 16	Garry deN. Hough, Jr., M.D.
Pittsfield	September 17	Edward J. Coughlin, Jr., M.D.
Worcester	September 19	John W. O'Meara, M.D.
Fall River	September 22	David S. Grice, M.D.
Hyannis	September 25	Paul L. Norton, M.D.

RHEUMATIC-FEVER CLINICS	DATES
Fitchburg	September 3, 10, 17, 24
North Reading	September 9, 16, 23, 30

PLASTIC CLINICS	HELD	CONSULTANT
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Callender's Surgical Anatomy. By Barry J. Anson, M.A., Ph.D. (M. Sc.), professor of anatomy, Northwestern University Medical School; and Walter G. Maddock, M.D., Elcock Professor of Surgery, Northwestern University Medical School. Third edition. 4°, cloth, 1074 pp., with 929 illustrations. Philadelphia: W. B. Saunders Company, 1952. $14.00.

The previous edition of this well known book was published in 1939. The text has been revised to bring it up to date, with the help of some of the late Dr. Callender's associates. There is a comprehensive index and the publishing is excellent. The book should be in all medical libraries.

Penicillin Decade, 1941–1951: Sensitizations and toxicities. By Lawrence W. Smith, M.D., medical director, Commercial Solvents Corporation; and Ann D. Walker, R.N. 8°, cloth, 122 pp. Washington, D. C.: Arundel Press, Incorporated, 1951. $2.50.

This small monograph discusses the use of penicillin in various disorders. There is a valuable list of 342 references to the literature.

The Genetics of Micro-Organisms. By D. G. Catcheside, reader in plant cytogenetics, University of Cambridge, and fellow of Trinity College, Cambridge. 8°, cloth, 223 pp., with 35 illustrations, frontispiece and 49 tables. New York: Pitman Publishing Corporation, 1951, $4.50.

This book is based on a course of lectures devised for biochemists. The preliminary chapters deal with mutation and the gene system, mutation and adaptation and the sexual reproductive systems. These are followed by chapters on the yeasts, protozoa, bacteria and viruses. The text is concluded with a bibliography arranged by subjects. The publishing is excellent, and the printing was done in Great Britain.

Einführung in die Röntgenologie: Ein Lehrbuch fur Ärzte und Studierende. By G. F. Haenisch, a.o. Prof. Dr. Med., Chefarzt i.r. am allgem. Krankenhaus Barmbeck, Hamburg; and H. Holthusen, o.ö. Prof. Dr. Med., Chefarzt am allgemeinen Krankenhaus St. Georg, Hamburg. Mit einem physikalischen-technischen Beitrag, von A. Liechti. Bearbeitet und Ergänzt von Dr. W. Fehr, Hamburg. Fifth revised edition. 4°, cloth, 521 pp., with 371 illustrations. Stuttgart: Georg Thieme, 1951. Ganzleinen DM 60. Distributed by Grune and Stratton, Incorporated, New York.

The first edition of this standard textbook of roentgenology was first published in 1933. This new edition has been revised and brought up to date. The text is divided into three parts: One, Physik und Technik; Two, Diagnostik; and Three, Therapie. The section on diagnosis is divided into general and special diagnosis. The special part discusses the bones and joints, including the skull, and the internal organs. Treatment is also subdivided into general and special. The work is based on the experience of the authors and has no list of references. It is comprehensive in scope and has a good index.

Acta Radiologica. Supplements.

No. 84. *Studies on the Hepatic Ducts in Cholangiography.* By Olof Norman. 4°, paper, 81 pp., with 41 illustrations and 2 plates. Stockholm, 1951. Sw. cr. 15.

In this monograph is given the technic as practised at the university clinics of Lund. The series discussed consisted of 46 verified cases of hepatic calculi, including 31 cases in which stones were visualized in the intrahepatic ducts. The period covered was from January 1, 1947, to June 30, 1950, during which operative cholangiography was performed on 919 patients.

No. 85. *Soft Tissue Radiography: Technical aspects and clinical applications in the examination of limbs.* By Arne Frantzell. 4°, paper, 103 pp., with 37 illustrations. Stockholm, 1951. Sw. cr. 20.

The text is divided into two parts; the first, of 66 pages, discusses the varying technical aspects in which Laurell's method is analyzed, and the second part presents examples of the image of the cutis and subcutis in healthy and in edematous and varicose persons. Four cases of dystrophia musculorum progressiva, in which the method was used, are described. The literature on the subject is analyzed briefly and a bibliography concludes the text.

No. 86. *Roentgen Examination of Pleural Fluid: A study of the localization of free effusions, the potentialities of diagnosing minimal quantities of fluid and its existence under physiological conditions.* By Ingemar Hessén. 4°, paper, 80 pp., with 98 illustrations and 5 tables. Stockholm, 1951. Sw. cr. 20.

Two methods for visualizing small amounts of fluid are described and the literature on the subject is reviewed. A bibliography is appended to the text.

No. 87. *Vertebral Angiography by Catheterization: A new method employed in 221 cases.* By Stig Radner. 4°, paper, 134 pp., with 68 illustrations. Stockholm, 1951. Sw. cr. 20.

The technic of catheterization and its performance are described and the results of 239 operations in 221 patients are given. Likewise, the technic of angiography after catheterization and the author's method are described. Special chapters are devoted to the normal and pathologic vertebral angiogram.

No. 88. *Transit Time through the Small Intestine: A roentgenologic study on normal variability.* By Lars Lönnerblad. 4°, paper, 85 pp., with 32 illustrations. Stockholm, 1951. Sw. cr. 20.

The literature is reviewed and the methods described; the transit time is given for various age groups from one-year-olds to eighteen to twenty-five years.

No. 89. *Thoracic Aortography: With special reference to its value in patent ductus arteriosus and coarctation of the aorta.* By Gunnar Jönsson, Bror Brodén and Johan Karnell. 4°, paper, 176 pp., illustrated. Stockholm, 1951. Sw. cr. 30.

This important study consists of 46 pages of text, the remainder of illustrations. There is a short historical survey of the subject and a bibliography of 2 pages.

The Specialties in General Practice. Edited by Russell L. Cecil, M.D. 4°, cloth, 818 pp., with 470 illustrations. Philadelphia: W. B. Saunders Company, 1951. $14.50.

This composite book is the joint work of fourteen specialists. The first three chapters deal with minor surgery, orthopedic surgery and fractures and dislocations. These are followed by urology, diseases of the anus, rectum and colon, gynecology and obstetrics, pediatrics, diseases of the nose, throat, larynx, bronchi and esophagus, otology, ophthalmology, dermatology and syphilology and psychiatry. The publishing is excellent and there is a comprehensive index. This is a working book and should prove valuable to the general practitioner.

NOTICES

ANNOUNCEMENT

Dr. Robert H. McCarter announces the removal of his office to 82 Marlborough Street, Boston.

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held on Wednesday, October 8, 1952, in Boston.

The usual clinical activities will be presented during the the day, with an evening meeting at Longwood Towers. Details of the program will be published at a later date.

AMERICAN ACADEMY OF DENTAL MEDICINE

The annual mid-winter meeting and luncheon of the American Academy of Dental Medicine will be held at the Hotel Statler, New York City, on Sunday, December 7, at 12:30 p.m. There will be a business meeting for members and delegates at 10:30 a.m. From 2 to 5 p.m., after the luncheon, there will be a symposium on "Pain," discussed by Drs. R. J. Behan, Theodore Blum and Samuel C. Miller, with Dr. Joseph L. Bernier acting as moderator. All members and interested dentists and physicians are cordially invited.

Reservations and programs may be obtained from Dr. J. Englander, 2616 Hudson Boulevard, Jersey City, New Jersey, or Dr. S. Turkenkopf, 196 Montclair Avenue, Newark, New Jersey.

PHI DELTA EPSILON LECTURE

The annual Phi Delta Epsilon Lecture of Sigma Chapter will be given on Wednesday, September 17, at 4 p.m., in the auditorium of Temple University School of Medicine in Philadelphia. Dr. Bernhard Zondek will speak on "Problems of Ovarian Function and Gonadal Hormones." All physicians and students are welcome.

AMERICAN DERMATOLOGICAL ASSOCIATION ANNUAL PRIZE ESSAY CONTEST

The American Dermatological Association is offering a prize of $300 for the best essay submitted for original work, not previously published, on some fundamental aspect of dermatology or syphilology. The purpose of this contest is to stimulate investigators to original work in these fields.

Manuscripts typed in English with double spacing and ample margins as for publication, together with illustrations, charts, and tables, are to be submitted in triplicate not later than January 1, 1953, and should be sent to Dr. Louis A. Brunsting, secretary, American Dermatological Association, 102-110 Second Avenue, Southwest, Rochester, Minnesota. The competition is open to scientists generally — not necessarily to physicians.

The prize-winning candidate may be invited to present his paper before the annual meeting of the American Dermatological Association June 9-13, 1953, at the Lake Placid Club, Essex County, New York, with expenses paid. Further information regarding this essay contest may be obtained from the secretary of the Association.

SOCIETY MEETINGS AND CONFERENCES

AUGUST 31–SEPTEMBER 6. Interamerican Congress of Cardiology. Page 522, issue of March 27.

SEPTEMBER 2–5. International College of Surgeons. Page 190, issue of July 31.

SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies. Mount Washington Hotel, Bretton Woods, New Hampshire.

SEPTEMBER 8–20. First Argentine Congress of Thoracic Surgery. Page 1024, issue of June 26.

SEPTEMBER 9. Springfield Academy of Medicine. Speaker Dr. W. B. Sherman, New York City.

SEPTEMBER 17. Phi Delta Epsilon Lecture. Notice above.

SEPTEMBER 23. Norfolk District Medical Society. Page 190, issue of July 31.

SEPTEMBER 24. Massachusetts Academy of General Practice. Fall meeting. Hotel Statler, Boston.

SEPTEMBER 26–28. Aero Medical Association. Page ix, issue of July 31.

OCTOBER 1. Essex North District Medical Society. Page 226, issue of August 7.

OCTOBER 1–3. Mississippi Valley Medical Society. Seventeenth Annual Meeting. Jefferson Hotel, St. Louis, Missouri. Page xiii, issue of August 21.

OCTOBER 1–3. American Medical Writers' Association. Page ix, issue of July 31.

OCTOBER 6–17. New York Academy of Medicine. Page xi, issue of July 24.

OCTOBER 8. New England Pediatric Society. Notice above.

OCTOBER 14. Springfield Academy of Medicine. Page 190, issue of July 31.

OCTOBER 18–23. American Academy of Pediatrics. Page xi, issue of July 24.

OCTOBER 28–30. New England Postgraduate Assembly. Hotel Statler, Boston.

OCTOBER 29. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

OCTOBER 30–NOVEMBER 1. National Association for Music Therapy. Page ix, issue of July 31.

OCTOBER 31 AND NOVEMBER 1. Eastern Section of American Trudeau Society. Page 190, issue of July 31.

(*Notices concluded on page ix*)